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Is Sleep Deprivation Useful in the Treatment of Depression?
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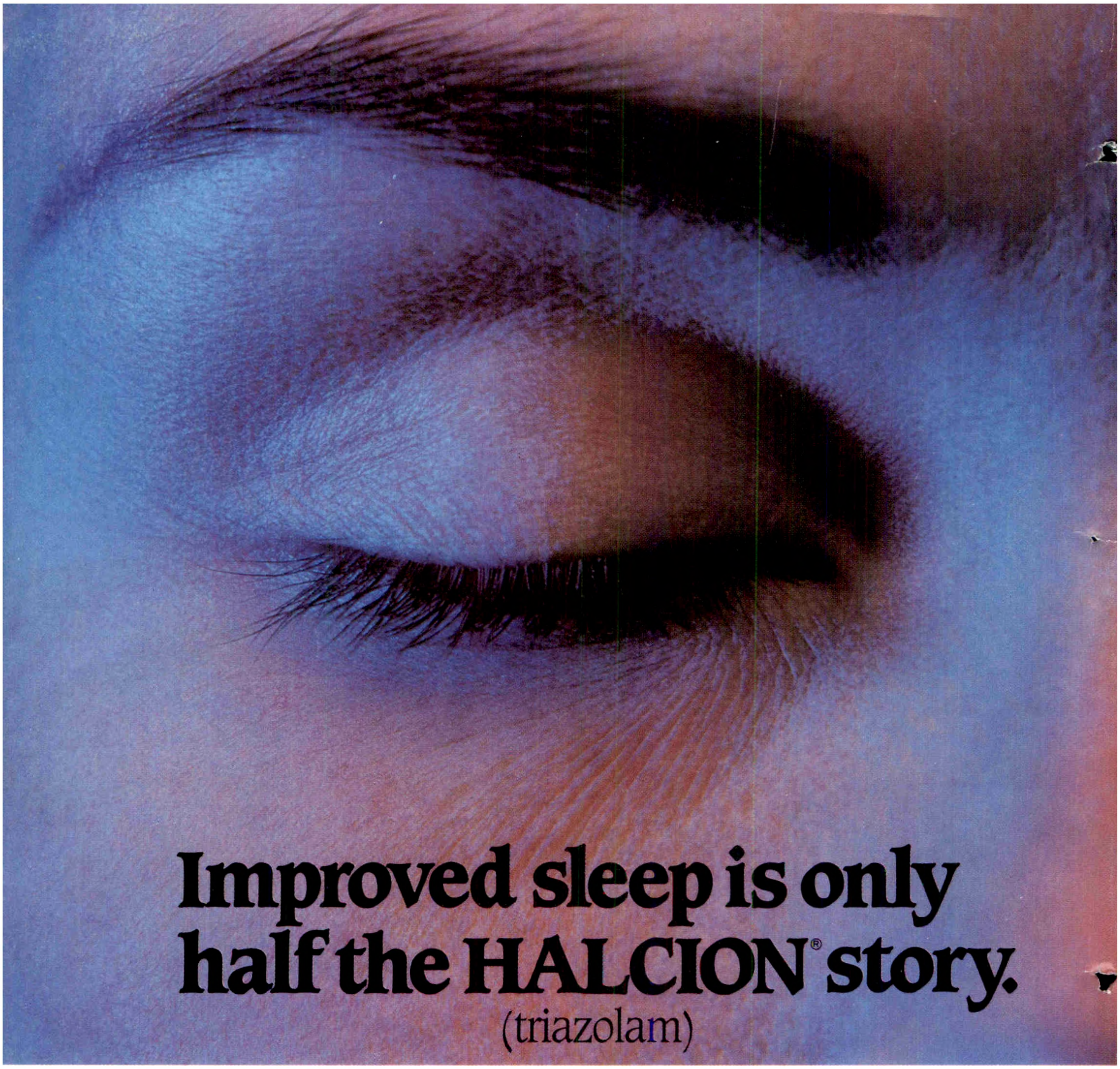
By James E. Spar and Andrew S. Garb

Official Journal of the American Psychiatric Association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## In depressed patients HALCION is effective when adjunctive insomnia therapy is required.

Disturbed sleep is not an uncommon problem in depressed patients, and although standard tricyclic antidepressants (TCAs) usually relieve insomnia, some depressed patients continue to experience its symptoms. The short-term use of HALCION to relieve insomnia refractory to treatment with TCAs has proven successful in two clinical evaluations.

### Effective, concomitant therapy.

HALCION was compared with placebo in a double-blind comparative study of 53 depressed outpatients who had been stabilized on a TCA for at least six weeks but who still suffered refractory insomnia. HALCION was shown to be more effective in relieving the symptoms of insomnia without making depressive symptoms worse.[1]

# Daytime alertness is the other half.

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In another double-blind study comparing HALCION with placebo in 78 depressed outpatients receiving 50-300 mg of imipramine per day, HALCION was significantly more effective in improving most sleep parameters. In addition, there was no evidence that HALCION interfered with the efficacy of imipramine or aggravated the patients' depressive symptoms.[2]

These studies suggest that HALCION is effective adjunctive therapy for the relief of short-term insomnia in depressed patients.

Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

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## Halcion® Tablets (triazolam, ⓒⅣ Upjohn)

**INDICATIONS AND USAGE:** HALCION Tablets are indicated for the short-term treatment of insomnia (generally 7 to 10 days). Use for more than 2 to 3 weeks requires complete patient reevaluation (see WARNINGS).

Prescriptions for HALCION should be written for short-term use (7 to 10 days), and it should not be prescribed in quantities exceeding a 1-month supply.

**CONTRAINDICATIONS:** Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

**WARNINGS:** A decision to initiate symptomatic treatment of insomnia should only be made after the patient and sleep disturbance have been carefully evaluated. The failure of insomnia to remit after 7 to 10 days may indicate the presence of a primary psychiatric and/or medical illness.

Worsening insomnia or the emergence of new abnormalities of thinking or behavior may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of HALCION.

Because some of the adverse effects of HALCION appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose. Elderly patients are especially susceptible to dose-related adverse effects.

An increase in daytime anxiety has been reported for HALCION after as few as 10 days of continuous use. In some patients, this may be a manifestation of interdose withdrawal. If increased daytime anxiety occurs during treatment, discontinuation of treatment may be advisable.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics, including HALCION. Some of these changes may be characterized by decreased inhibition, eg, aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (eg, sedatives/hypnotics). Other kinds of behavior changes have also been reported, eg, bizarre behavior, agitation, hallucinations, and depersonalization. The worsening of depression, including suicidal thinking, has been reported in primarily depressed patients in association with the use of benzodiazepines.

The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS-depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines. Data suggest that anterograde amnesia may occur at a higher rate with HALCION than with other benzodiazepine hypnotics.

**PRECAUTIONS:** *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, light-headedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but evidence is inconclusive. Therapy should be initiated at the lowest effective dose. "Traveler's amnesia" has been reported when HALCION was taken to induce sleep while traveling. Caution should be exercised in patients with signs or symptoms of depression, which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage are more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function, chronic pulmonary insufficiency, and sleep apnea. *Information for Patients* (see patient package insert for full information): Alert patients about (1) how, when, and how long to take HALCION, (2) not extending use of HALCION beyond 7 to 10 days without consulting physician, (3) the need to discuss with physician any unusual or disturbing thoughts or behavior that develop during treatment, (4) consumption of alcohol and drugs, (5) not taking HALCION when a full night's sleep and clearance from the body is not possible before they need to be active and functional, eg, an overnight flight of less than 7 to 8 hours, (6) not increasing prescribed dose, (7) not operating machinery or driving, (8) possible worsening of sleep after discontinuing HALCION, and (9) possible fetal abnormalities. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS-depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, eg, coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam. Therefore, increased clinical observation and consideration of dose reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother on benzodiazepines may have withdrawal symptoms and neonatal flaccidity postnatally. *Nursing Mothers:* Administration is not recommended.

*Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

**ADVERSE REACTIONS:** During placebo-controlled clinical studies involving 1,003 patients treated with HALCION, the most troublesome side effects were extensions of the pharmacologic activity, eg, drowsiness (14% of patients). Other side effects reported by 4% to 10% of patients were headache, dizziness, nervousness, light-headedness, coordination disorder/ataxia, nausea, and vomiting.

Adverse events reported less frequently (ie, 0.5% to 0.9%) were euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (ie, less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: amnestic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Other events reported include paradoxical reactions such as stimulation, mania, agitation, increased muscle spasticity, sleep disturbances, hallucinations, delusions, aggressiveness, falling, somnambulism, syncope, inappropriate behavior, and other adverse behavioral effects. Should these occur, the drug should be discontinued. Other reported events: chest pain, burning tongue/glossitis/stomatitis.

No laboratory changes were considered to be of physiologic significance.

When treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Minor changes in EEG patterns, of no known significance, have been observed in patients during therapy with HALCION.

**DRUG ABUSE AND DEPENDENCE:** *Controlled Substance:* HALCION Tablets are a Controlled Substance, Schedule IV. *Abuse, Dependence, and Withdrawal:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines given for as few as 1 to 2 weeks; and, in some patients, there may be withdrawal symptoms (daytime anxiety, agitation) between nightly doses. Abrupt discontinuation should be avoided, and gradual dosage tapering is recommended for any patient taking more than the lowest dose more than a few weeks. Patients with a history of seizures are at particular risk. Dependence-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

**OVERDOSAGE:** Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiratory depression, apnea, seizures, and death have been reported. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

**DOSAGE AND ADMINISTRATION:** The dosage of HALCION Tablets must be individualized and the lowest effective dose used. The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be sufficient for some patients (eg, low body weight). Because the risk of several adverse reactions increases with dose size, a dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose. A dose of 0.5 mg should not be exceeded.

In geriatric and/or debilitated patients, the dosage range is 0.125 to 0.25 mg. Therapy should be initiated at 0.125 mg, and the 0.25-mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

**HOW SUPPLIED:** HALCION Tablets are available as 0.125-mg and 0.25-mg tablets.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription. B-8-S

**Reference:**

1. Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
2. Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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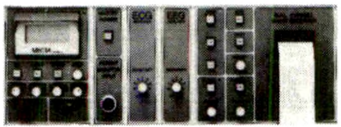

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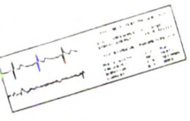

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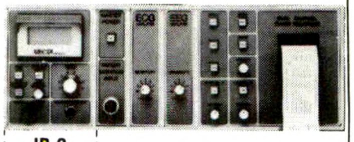

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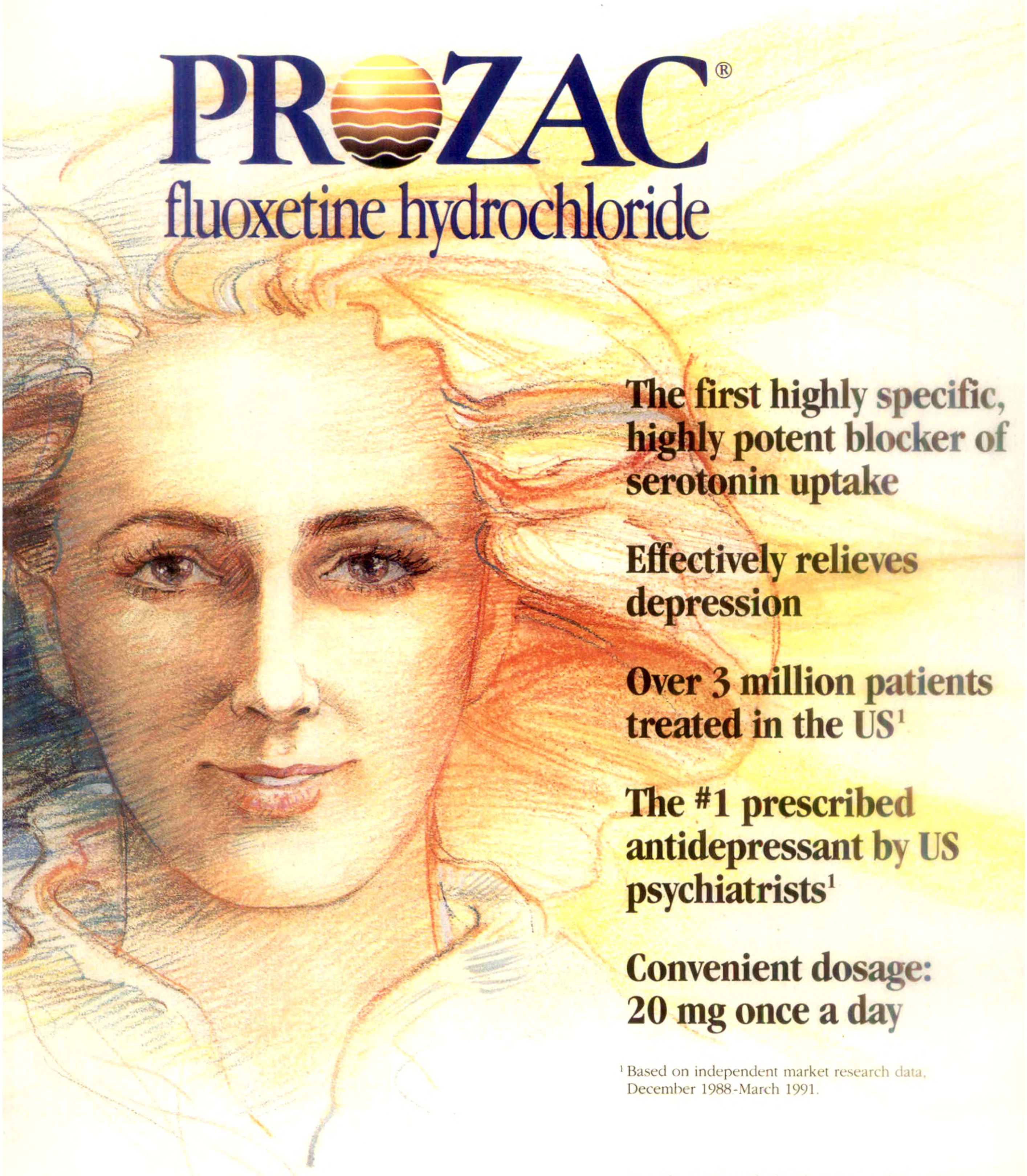

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**Brief Summary. Consult the package insert for complete prescribing information.**

**Indication:** For the treatment of depression.

**Contraindications:** Known hypersensitivity to Prozac.

*Monoamine Oxidase Inhibitors* — There have been reports of serious, sometimes fatal, reactions in patients receiving fluoxetine in combination with an MAOI and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

Wait at least 14 days between discontinuing an MAOI and starting therapy with Prozac. Because of the long half-lives of fluoxetine and its active metabolite, wait at least 5 weeks between discontinuing Prozac and starting therapy with an MAOI. Prozac should not be used concomitantly with MAOIs.

**Warnings:** *Rash and Possibly Allergic Events* — Approximately 4% of 5,600 fluoxetine patients developed a rash and/or urticaria in premarketing testing. Almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of 2 patients who developed a serious cutaneous systemic illness during premarketing clinical trials, 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or represent immunologic responses is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

**Precautions:** *General* — Anxiety, Nervousness, and Insomnia — Reported by 10% to 15% of patients, 5% of whom discontinued fluoxetine.

Altered Appetite and Weight — Significant weight loss, especially in underweight patients, may be an undesirable result of treatment.

Approximately 9% of fluoxetine patients experienced anorexia in controlled clinical trials, an incidence approximately sixfold that seen with placebo. A weight loss >5% of body weight occurred in 13% of fluoxetine patients compared with 4% in those on placebo and 3% in those on tricyclics. However, only rarely did fluoxetine patients discontinue treatment because of weight loss.

Activation of Mania/Hypomania — Hypomania or mania occurred in approximately 1% of fluoxetine patients in premarketing testing.

Seizures — Twelve of 6,000 patients (0.2%) experienced convulsions (or, possibly, seizures). Prozac should be introduced with care in patients with a history of seizures.

Suicide — Close supervision of high-risk patients should accompany initial therapy. Prescriptions of Prozac should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (2 to 3 days) and its major active metabolite (7 to 9 days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

Use in Patients with Concomitant Illness — Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. ECGs of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis, the clearances of fluoxetine and its active metabolite were decreased. A lower or less frequent dose should be used in patients with cirrhosis.

Fluoxetine should be used with caution in patients with severe renal impairment.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when fluoxetine therapy is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.

*Information for Patients* — Physicians should advise their patients to notify them if they:

- are taking or plan to take any prescription or over-the-counter drugs or alcohol
- become pregnant or intend to become pregnant during therapy
- are breast feeding an infant
- develop a rash or hives

*Drug Interactions* — Tryptophan — Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Contraindications.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents.

Lithium — There have been reports of both increased and decreased lithium levels and lithium toxicity. Lithium levels should be monitored.

Diazepam Clearance — The half-life of diazepam may be prolonged in some patients.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the concurrent administration of fluoxetine and another tightly bound drug may cause a shift in plasma concentrations potentially resulting in an adverse effect. Adverse effects may also result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs — Caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy — There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

*Carcinogenesis, Mutagenesis, Impairment of Fertility* — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for 2 years at doses approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively revealed no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies in rats at doses approximately 5 and 9 times the maximum human dose (80 mg) respectively revealed no adverse effects on fertility. A slight decrease in neonatal survival was noted, probably associated with depressed maternal food consumption and suppressed weight gain.

*Pregnancy* — Teratogenic Effects — Pregnancy Category B — Reproduction studies in rats and rabbits at doses 9 and 11 times the maximum human dose (80 mg) respectively revealed no evidence of harm to the fetus. Although there have been no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed.

*Labor and Delivery* — The effect of Prozac on labor and delivery in humans is unknown.

*Nursing Mothers* — Because Prozac is known to be excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

*Usage in Children* — Safety and effectiveness in children have not been established.

*Usage in the Elderly* — In clinical studies of several hundred elderly patients, no unusual adverse age-related phenomena were identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.

*Hyponatremia* — Hyponatremia (some cases with serum Na <110 mmol/L) has been reported, which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or otherwise volume depleted.

*Platelet Function* — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

**Adverse Reactions:** *Commonly Observed* — Nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

*Associated With Discontinuation of Treatment* — Fifteen percent of 4,000 clinical trial patients discontinued fluoxetine due to an adverse event. The more common events included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

*Incidence in Controlled Clinical Trials* — The accompanying table enumerates adverse events that occurred at a frequency of ≥ 1% in controlled trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE
IN PLACEBO-CONTROLLED CLINICAL TRIALS

| | Percentage of Patients Reporting Event | | | Percentage of Patients Reporting Event | |
|---|---|---|---|---|---|
| Body System/ Adverse Event* | Prozac (N = 1,730) | Placebo (N = 799) | Body System/ Adverse Event* | Prozac (N=1,730) | Placebo (N=799) |
| **Nervous** | | | **Body as a Whole** | | |
| Headache | 20.3 | 15.5 | Asthenia | 4.4 | 1.9 |
| Nervousness | 14.9 | 8.5 | Infection, viral | 3.4 | 3.1 |
| Insomnia | 13.8 | 7.1 | Pain, limb | 1.6 | 1.1 |
| Drowsiness | 11.6 | 6.3 | Fever | 1.4 | — |
| Anxiety | 9.4 | 5.5 | Pain, chest | 1.3 | 1.1 |
| Tremor | 7.9 | 2.4 | Allergy | 1.2 | 1.1 |
| Dizziness | 5.7 | 3.3 | Influenza | 1.2 | 1.5 |
| Fatigue | 4.2 | 1.1 | **Respiratory** | | |
| Sedated | 1.9 | 1.3 | Upper respiratory infection | 7.6 | 6.0 |
| Sensation disturbance | 1.7 | 2.0 | Flu-like syndrome | 2.8 | 1.9 |
| Libido, decreased | 1.6 | — | Pharyngitis | 2.7 | 1.3 |
| Light-headedness | 1.6 | — | Nasal congestion | 2.6 | 2.3 |
| Concentration, decreased | 1.5 | — | Headache, sinus | 2.3 | 1.8 |
| **Digestive** | | | Sinusitis | 2.1 | 2.0 |
| Nausea | 21.1 | 10.1 | Cough | 1.6 | 1.6 |
| Diarrhea | 12.3 | 7.0 | Dyspnea | 1.4 | — |
| Mouth dryness | 9.5 | 6.0 | **Cardiovascular** | | |
| Anorexia | 8.7 | 1.5 | Hot flushes | 1.8 | 1.0 |
| Dyspepsia | 6.4 | 4.3 | Palpitations | 1.3 | 1.4 |
| Constipation | 4.5 | 3.3 | **Musculoskeletal** | | |
| Pain, abdominal | 3.4 | 2.9 | Pain, back | 2.0 | 2.4 |
| Vomiting | 2.4 | 1.3 | Pain, joint | 1.2 | 1.1 |
| Taste change | 1.8 | — | Pain, muscle | 1.2 | 1.0 |
| Flatulence | 1.6 | 1.1 | **Urogenital** | | |
| Gastroenteritis | 1.0 | 1.4 | Menstruation, painful | 1.9 | 1.4 |
| **Skin and Appendages** | | | Sexual dysfunction | 1.9 | — |
| Sweating, excessive | 8.4 | 3.8 | Frequent micturition | 1.6 | — |
| Rash | 2.7 | 1.8 | Urinary tract infection | 1.2 | — |
| Pruritus | 2.4 | 1.4 | **Special Senses** | | |
| | | | Vision disturbance | 2.8 | 1.8 |

*Events reported by ≥1% of fluoxetine patients are included.
— Incidence <1%

*Other Events Observed During Premarketing Evaluation in 5,600 Fluoxetine Patients* — Frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first-degree, bradycardia, bundle branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

*Postintroduction Reports* — Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: aplastic anemia, cerebral vascular accident, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), ecchymoses, eosinophilic pneumonia, gastrointestinal hemorrhage, hyperprolactinemia, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

**Overdosage**: *Human Experience* — As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. A second death involved fluoxetine, codeine, and temazepam.

One other patient who reportedly took 3,000 mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the 2 deaths noted above, all other overdose cases recovered without residua.

A single death attributed to overdose of fluoxetine alone has been reported.

PV 2473 DPP [072491]

*Additional information available to the profession upon request.*

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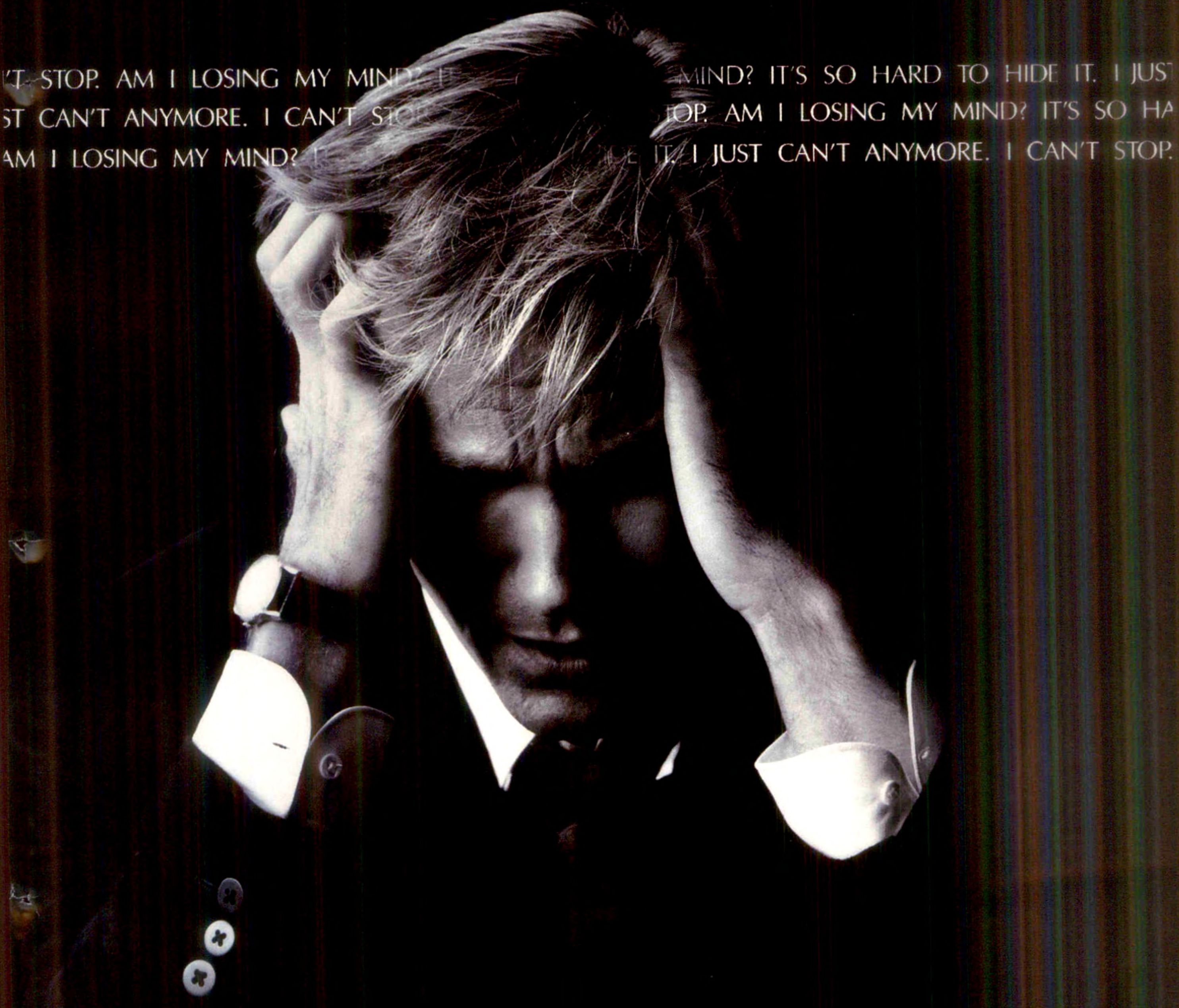
**Dista Products Company**
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

FL-4931-T-149317

# Powerful medicine to stop intrusive thoughts and acts


T STOP. AM I LOSING MY MIND? I… MIND? IT'S SO HARD TO HIDE IT. I JUS
ST CAN'T ANYMORE. I CAN'T STO… TOP. AM I LOSING MY MIND? IT'S SO HA
AM I LOSING MY MIND? I… E IT. I JUST CAN'T ANYMORE. I CAN'T STOP.

*25 • 50 • 75-mg capsules*

# Anafranil®

*clomipramine HCl*

## *Powerful tricyclic therapy for obsessive-compulsive disorder*

▲ *Symptoms are substantially reduced in 60% of patients*[1]*

***Reduces anxiety-producing intrusive thoughts***[2]

***Reduces ritualized behavior***[2]

▲ *Dual mode of action creates a unique treatment role*

*Anafranil is believed to block the reuptake of serotonin and norepinephrine.*[3,4]

▲ *Safety and tolerability demonstrated in over 20 years of worldwide use**

**The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See Warnings and full Prescribing Information on page 4.*

**BASEL**
**Pharmaceuticals**

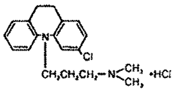
***References:* 1.** *Data on file, CIBA-GEIGY Corporation.* **2.** *DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine.* Psychiatr Ann. *1989;19:97-101.* **3.** *Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline.* Arch Gen Psychiatry. *1983;40:605-611.* **4.** *Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder.* Arch Gen Psychiatry. *1988;45:167-171.*

# Anafranil®
## clomipramine hydrochloride
## Capsules

## Prescribing Information

### DESCRIPTION
Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

*Inactive Ingredients*. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

### CLINICAL PHARMACOLOGY
#### Pharmacodynamics
Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

#### Pharmacokinetics
***Absorption/Bioavailability:*** CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations ($C_{ss}$) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although $C_{ss}$ and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher $C_{ss}$ and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

***Distribution:*** CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

***Metabolism:*** CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

***Elimination:*** Evidence that the $C_{ss}$ and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

*Interactions:* Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly lower in smokers than in nonsmokers.

### INDICATIONS AND USAGE
Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

### CONTRAINDICATIONS
Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

### WARNINGS
#### Seizures
During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7% (25 of 3519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between Anafranil treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

### PRECAUTIONS
#### General
***Suicide:*** Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

***Cardiovascular Effects:*** Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

***Psychosis, Confusion, And Other Neuropsychiatric Phenomena:*** Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

***Mania/Hypomania:*** During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

***Hepatic Changes:*** During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

***Hematologic Changes:*** Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

***Central Nervous System:*** More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

***Sexual Dysfunction:*** The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

***Weight Changes:*** In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

***Electroconvulsive Therapy:*** As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

***Surgery:*** Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

***Use in Concomitant Illness:*** As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;
4. Patients with significantly impaired renal function.

***Withdrawal Symptoms:*** A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

#### Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS);
2. The relatively high incidence of sexual dysfunction among males (see Sexual Dysfunction);
3. Since Anafranil may impair the mental and/or physical abilities required for the performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);
4. Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs;
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
6. Patients should notify their physician if they are breast-feeding.

#### Drug Interactions
The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see Information for Patients). Anafranil should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

#### Pregnancy Category C
No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Nursing Mothers
Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use
In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

#### Use in Elderly
Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

### ADVERSE REACTIONS
#### Commonly Observed
The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

#### Leading to Discontinuation of Treatment
Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

#### Incidence in Controlled Clinical Trials
The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) or placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

### Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting Event)

| | Adults | | Children and Adolescents | |
|---|---|---|---|---|
| **Body System/ Adverse Event*** | **Anafranil (N=322)** | **Placebo (N=319)** | **Anafranil (N=46)** | **Placebo (N=44)** |
| **Nervous System** | | | | |
| Somnolence | 54 | 16 | 46 | 11 |
| Tremor | 54 | 2 | 33 | 2 |
| Dizziness | 54 | 14 | 41 | 14 |
| Headache | 52 | 41 | 28 | 34 |
| Insomnia | 25 | 15 | 11 | 7 |
| Libido change | 21 | 3 | — | — |
| Nervousness | 18 | 2 | 4 | 2 |
| Myoclonus | 13 | — | 2 | — |
| Increased appetite | 11 | 2 | — | 2 |
| Paresthesia | 9 | 3 | 2 | 2 |
| Memory impairment | 9 | 1 | 7 | 2 |
| Anxiety | 9 | 4 | 2 | — |
| Twitching | 7 | 1 | 4 | 5 |
| Impaired concentration | 5 | 2 | — | — |
| Depression | 5 | 1 | — | — |
| Hypertonia | 4 | 1 | 2 | — |
| Sleep disorder | 4 | — | 9 | 5 |
| Psychosomatic disorder | 3 | — | — | — |
| Yawning | 3 | — | — | — |
| Confusion | 3 | — | 2 | — |
| Speech disorder | 3 | — | — | — |
| Abnormal dreaming | 3 | — | — | 2 |
| Agitation | 3 | — | — | — |
| Migraine | 3 | — | — | — |
| Depersonalization | 2 | — | 2 | — |
| Irritability | 2 | 2 | 2 | — |
| Emotional lability | 2 | — | — | 2 |
| Panic reaction | 1 | — | 2 | — |
| Aggressive reaction | — | — | 2 | — |
| Paresis | — | — | 2 | — |
| **Skin and Appendages** | | | | |
| Increased sweating | 29 | 3 | 9 | — |
| Rash | 8 | 1 | 4 | 2 |
| Pruritus | 6 | — | 2 | 2 |
| Dermatitis | 2 | — | — | 2 |
| Acne | 2 | 2 | — | 5 |
| Dry skin | 2 | — | — | 5 |
| Urticaria | 1 | — | — | — |
| Abnormal skin odor | — | — | 2 | — |
| **Digestive System** | | | | |
| Dry mouth | 84 | 17 | 63 | 16 |
| Constipation | 47 | 11 | 22 | 9 |
| Nausea | 33 | 14 | 9 | 11 |
| Dyspepsia | 22 | 10 | 13 | 2 |
| Diarrhea | 13 | 9 | 7 | 5 |
| Anorexia | 12 | — | 22 | 2 |
| Abdominal pain | 11 | 9 | 13 | 16 |
| Vomiting | 7 | 2 | 7 | — |
| Flatulence | 6 | 3 | — | 2 |
| Tooth disorder | 5 | — | — | — |
| Gastrointestinal disorder | 2 | — | — | 2 |
| Dysphagia | 2 | — | — | — |
| Esophagitis | 1 | — | — | — |
| Eructation | — | — | 2 | 2 |
| Ulcerative stomatitis | — | — | 2 | — |
| **Body as a Whole** | | | | |
| Fatigue | 39 | 18 | 35 | 9 |
| Weight increase | 18 | 1 | 2 | — |
| Flushing | 8 | — | 7 | — |
| Hot flushes | 5 | — | 2 | — |
| Chest pain | 4 | 4 | 7 | — |
| Fever | 4 | — | 2 | 7 |
| Allergy | 3 | 3 | 7 | 5 |
| Pain | 3 | 2 | 4 | 2 |
| Local edema | 2 | 4 | — | — |
| Chills | 2 | 1 | — | — |
| Weight decrease | — | — | 7 | — |
| Otitis media | — | — | 4 | 5 |
| Asthenia | — | — | 2 | — |
| Halitosis | — | — | 2 | — |
| **Cardiovascular System** | | | | |
| Postural hypotension | 6 | — | 4 | — |
| Palpitation | 4 | 2 | 4 | — |
| Tachycardia | 4 | — | 2 | — |
| Syncope | — | — | 2 | — |
| **Respiratory System** | | | | |
| Pharyngitis | 14 | 9 | — | 5 |
| Rhinitis | 12 | 10 | 7 | 9 |
| Sinusitis | 6 | 4 | 2 | 5 |
| Coughing | 6 | 6 | 4 | 5 |
| Bronchospasm | 2 | — | 7 | 2 |
| Epistaxis | 2 | — | — | 2 |
| Dyspnea | — | — | 2 | — |
| Laryngitis | — | 1 | 2 | — |
| **Urogenital System** | | | | |
| **Male and Female Patients Combined** | | | | |
| Micturition disorder | 14 | 2 | 4 | 2 |
| Urinary tract infection | 6 | 1 | — | — |
| Micturition frequency | 5 | 3 | — | — |
| Urinary retention | 2 | — | 7 | — |
| Dysuria | 2 | 2 | — | — |
| Cystitis | 2 | — | — | — |
| **Female Patients Only** | (N=182) | (N=167) | (N=10) | (N=21) |
| Dysmenorrhea | 12 | 14 | 10 | 10 |
| Lactation (nonpuerperal) | 4 | — | — | — |
| Menstrual disorder | 4 | 2 | — | — |
| Vaginitis | 2 | — | — | — |
| Leukorrhea | 2 | — | — | — |
| Breast enlargement | 2 | — | — | — |
| Breast pain | 1 | — | — | — |
| Amenorrhea | 1 | — | — | — |
| **Male Patients Only** | (N=140) | (N=152) | (N=36) | (N=23) |
| Ejaculation failure | 42 | 2 | 6 | — |
| Impotence | 20 | 3 | — | — |
| **Special Senses** | | | | |
| Abnormal vision | 18 | 4 | 7 | 2 |
| Taste perversion | 8 | — | 4 | — |
| Tinnitus | 6 | — | 4 | — |
| Abnormal lacrimation | 3 | 2 | — | — |
| Mydriasis | 2 | — | — | — |
| Conjunctivitis | 1 | — | — | — |
| Anisocoria | — | — | 2 | — |
| Blepharospasm | — | — | 2 | — |
| Ocular allergy | — | — | 2 | — |
| Vestibular disorder | — | — | 2 | 2 |
| **Musculoskeletal** | | | | |
| Myalgia | 13 | 9 | — | — |
| Back pain | 6 | 6 | — | — |
| Arthralgia | 3 | 5 | — | — |
| Muscle weakness | 1 | — | 2 | — |
| **Hemic and Lymphatic** | | | | |
| Purpura | 3 | — | — | — |
| Anemia | — | — | 2 | 2 |
| **Metabolic and Nutritional** | | | | |
| Thirst | 2 | 2 | — | 2 |

*Events reported by at least 1% of Anafranil patients are included

**Other Events Observed During the Premarketing Evaluation of Anafranil**

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

***Body as a Whole:*** *Infrequent* — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

***Cardiovascular System:*** *Infrequent* — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

***Digestive System:*** *Infrequent* — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

***Endocrine System:*** *Infrequent* — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

***Hemic and Lymphatic System:*** *Infrequent* — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

***Metabolic and Nutritional Disorder:*** *Infrequent* — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

***Musculoskeletal System:*** *Infrequent* — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

***Nervous System:*** *Frequent* — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

***Respiratory System:*** *Infrequent* — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

***Skin and Appendages:*** *Infrequent* — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

***Special Senses:*** *Infrequent* — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

***Urogenital System:*** *Infrequent* — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

## DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

## OVERDOSAGE

### Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

### Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

### Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery.

In the alert patient, the stomach should be emptied promptly by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions. If anticonvulsants are necessary, diazepam and phenytoin may be useful. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, and, if necessary, a vasopressor agent by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

The slow intravenous administration of physostigmine salicylate has been used as a last resort to reverse severe CNS anticholinergic manifestations of overdosage with tricyclic antidepressants; however, it should not be used routinely since it may induce seizures and cholinergic crises.

## DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of the initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

### Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

### Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

### Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

## HOW SUPPLIED

| | |
|---|---|
| *Capsules 25 mg* — ivory/melon yellow (imprinted ANAFRANIL 25 mg) | |
| Bottles of 100 | NDC 58887-115-30 |
| Unit Dose (blister pack) | |
| Box of 100 (strips of 10) | NDC 58887-115-32 |
| *Capsules 50 mg* — ivory/aqua blue (imprinted ANAFRANIL 50 mg) | |
| Bottles of 100 | NDC 58887-116-30 |
| Unit Dose (blister pack) | |
| Box of 100 (strips of 10) | NDC 58887-116-32 |
| *Capsules 75 mg* — ivory/yellow (imprinted ANAFRANIL 75 mg) | |
| Bottles of 100 | NDC 58887-117-30 |
| Unit Dose (blister pack) | |
| Box of 100 (strips of 10) | NDC 58887-117-[illegible] |

Samples, when available, are identified by the word *SAMPLE* appearing on each capsule.

Do not store above 86°F (30°C). Protect from moisture.

*Dispense in tight container (USP).*

## ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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By Susan L. McElroy, James I. Hudson, Harrison G. Pope, Jr., et al.

# Calendar

*For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.*

## APRIL

April 2–5, 10th Annual Symposium in Forensic Psychiatry, American College of Forensic Psychiatry, San Francisco. Contact: Ed Miller, Executive Director, 26701 Quail Creek, Suite 295, Laguna Hills, CA 92656; 714-831-0236.

April 9–12, 12th National Conference on Anxiety Disorders, Anxiety Disorders Association of America, Houston. Contact: Conference Department, 6000 Executive Blvd., Rockville, MD 20852-3801; 301-231-5484.

April 12–17, conference, "Folk Medicine of Central America," Southern California Neuropsychiatric Institute, San Jose, Costa Rica. Contact: Ann McCormick, SCNPI, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102 (tel), 619-454-2104 (fax).

April 24–25, conference, "Women," Cambridge Hospital and Harvard Medical School, Boston. Contact: Judy Reiner Platt, Cambridge Hospital, 1493 Cambridge St., Cambridge, MA 02139; 617-864-6165.

April 26, 4th Annual Symposium on Treatment of Headaches and Facial Pain, Downstate Headache Center, New York. Contact: Alexander Mauskop, M.D., Director, The Downstate Headache Center, 132 Atlantic Avenue, Brooklyn Heights, NY 11201; 718-935-9666.

## MAY

May 2–7, 145th Annual Meeting, American Psychiatric Association, Washington, D.C. Contact: George Campbell, Director, Meetings Management, APA, 1400 K Street, N.W., Washington, DC 20005; 202-682-6193.

May 6–10, "Spring Symposium on Back Pain" (maximum of 24 hours of CME category 1 credit), American Back Society, Columbia Regional Hospital, and Columbia Spine Center, New Orleans. Contact: Aubrey A. Swartz, M.D., Executive Director, American Back Society, 2647 E. 14th Street, Suite 401, Oakland, CA 94601; 510-536-9929 (tel), 510-536-1812 (fax).

May 8–10, international congress, International Association Autism Europe, The Hague. Contact: Mies Hoffmann, The General Secretary IAAE, Rue Emile Leger 4, B-6320 Villers-la-Ville, Belgium; 32-71-879594.

May 24–27, 27th Annual Conference of the Association for the Care of Children's Health, "Building on the Strengths of Children and Families: Child Health Policy, Programs, and Practice," Atlanta. Contact: Lee Ann Slayton, ACCH, 7910 Woodmont Ave., Suite 300, Bethesda, MD 20814-3015; 301-654-1205.

May 27–30, regional symposium, World Psychiatric Association, Palermo, Italy. Contact: WPA Secretariat, c/o Clinica Lopez-Ibor, 44 Calle Nueva Zelanda, E-28035 Madrid, Spain; 34-1-3162740.

May 28–29, conference, "Psychiatric, Psychosocial and Ethical Aspects of Organ Transplantation," University of Pittsburgh School of Medicine and the Academy of Psychosomatic Medicine, Pittsburgh. Contact: Paula T. Trzepacz, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213; 412-624-0701.

May 29–31, conference, "1992: Update in Psychiatry," Medical University of South Carolina, Institute of Psychiatry, Charleston, South Carolina. Contact: the Psychiatry Resource Development Office, 171 Ashley Avenue, Charleston, SC, 29425-0742; 803-792-4012.

## JUNE

June 3–5, symposium, "Integrated Approach to Schizophrenia," Turku. Contact: Ulla Halkola, Congress Secretariat, University of Turku, Centre for Expansion Studies, Pispalantie 7, Turku 20510, Finland; 358-21-6336217.

June 11–14, 40th Annual Convention and Workshops, "Well-Being: Theory and Practice," North American Society of Adlerian Psychology, Chicago. Contact: Linda L. Wise, Convention Coordinator, 5353 Manhattan Circle, Suite 103, Boulder, CO 80303; 303-499-2299 (tel), 303-499-2599 (fax).

June 12–13, conference, "Psychotherapy," Cambridge Hospital and Harvard Medical School, Boston. Contact: Judy Reiner Platt, Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139; 617-864-6165.

June 21–26, conference, "Trauma and Tragedy: The Origins, Management and Prevention in Today's World," International Society for Traumatic Stress Studies, Amsterdam. Contact: Jos M.P. Weerts, Secretary, Organizing Committee, ICODO, P.B. 13362, 3507 LJ Utrecht, The Netherlands; (+31)(0)30-369312 (tel), (+31)(0)30-369037 (fax).

June 28–July 2, 18th Collegium Internationale Neuro-Psychopharmacologicum, Nice. Contact: Organizing Secretariat, Nice Congres, 1 Esplanade Kennedy, 06300 Nice, France; 33-93-928071

# Take a New Look at PAMELOR

## Clinical improvement in depression…

| With Anxiety | With Insomnia | In the Elderly |
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| 72% | 78% | 80%[1] |
| With little likelihood of agitation | With little daytime sedation | Most extensively studied and best-tolerated tricyclic antidepressant in the elderly[2] |

- Unlike serotonin reuptake inhibitors, PAMELOR does not commonly cause agitation, insomnia, or nausea[3]
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PAMELOR® (nortriptyline HCl) may impair the mental and/or physical abilities required for the performance of hazardous tasks; therefore, the patient should be warned accordingly. Because of its anticholinergic activity, PAMELOR therapy should be used with great caution in patients who have glaucoma or a history of urinary retention. As with all other antidepressants, patients with cardiovascular disease should be given PAMELOR therapy only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time.

Please see brief summary of prescribing information on last page of this advertisement.

**PAMELOR®**
**(nortriptyline HCl)**

CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL with alcohol content 4%

Proven Performance in Depression

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References

1. Georgotas A, McCue RE, Cooper TB, et al. How effective and safe is continuation therapy in elderly depressed patients? *Arch Gen Psychiatry*. 1988;45:929-932.
2. Katz IR, Curlik S, Lesher EL. Use of antidepressants in the frail elderly. *Clin Geriatr Med*. 1988;4(1):203-222.
3. Gelenberg AJ. The clinician's challenge: Strategies for treatment of depression in the 1990s. *J Clin Psychiatry*. 1991;52(6[suppl, second printing]):68-69.

## PAMELOR® (nortriptyline HCl)

**BRIEF SUMMARY:** Please see package insert for full prescribing information.

### CONTRAINDICATIONS

1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

### WARNINGS

Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

*Use in Pregnancy* — Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of child-bearing potential, the potential benefits must be weighed against the possible hazards.

*Use in Children* — Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

### PRECAUTIONS

Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

### ADVERSE REACTIONS

*Cardiovascular* — Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. ***Psychiatric*** — Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. ***Neurologic*** — Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. ***Anticholinergic*** — Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. ***Allergic*** — Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. ***Hematologic*** — Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. ***Gastrointestinal*** — Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. ***Endocrine*** — Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. ***Other*** — Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. ***Withdrawal Symptoms*** — Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

### OVERDOSAGE

Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage

[JULY 1, 1990 PAM-Z21]

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# THE MANFRED S. GUTTMACHER AWARD

The American Psychiatric Association and the American Academy of Psychiatry and the Law invite submissions for the 1993 Manfred S. Guttmacher Award. This award is given for an outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work presented at a professional meeting or published between May 1, 1991 and April 30, 1992. The award will be formally presented in May 1993 at the American Academy of Psychiatry and the Law meeting held in conjunction with the American Psychiatric Association Annual Meeting in San Francisco, CA. The award includes an honorarium of $500 and a plaque. The travel expenses of non-member winners will be reimbursed up to $500. The recipient is expected to present an award lecture. The award will be cited in the Convocation of Fellows program of the 1993 APA Annual Meeting and the lecture will be listed in the APA Convocation Program.

Anyone wishing to apply should submit 6 copies of the work, along with 6 copies of an abstract, to:

*W. Walter Menninger, M.D.*
*Chairman*
*Guttmacher Award Board*
*American Psychiatric Association*
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Entries must be recieved by May 15, 1992. Entries will be acknowledged but not returned.

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XANAX IS THE FIRST AND ONLY MEDICATION INDICATED FOR PANIC DISORDER

- Usually blocks panic attacks, often within the first week of therapy[1]
- No cardiovascular toxicity

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| Usual starting dosage for panic disorder | 0.5 mg tid |
| Average dosage in clinical studies at week 8 | 5.7 mg/day |

Side effects reported with XANAX are those generally associated with benzodiazepine therapy, such as drowsiness and impaired coordination.

XANAX 2-mg MULTISCORED TABLETS FOR COST-EFFECTIVE THERAPY

**Reference**
1. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial, I: efficacy in short-term treatment. *Arch Gen Psychiatry.* 1988;45:413-422.

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Tablets
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**First for Panic**

Please see adjacent page for brief summary of prescribing information.

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# Xanax®
# alprazolam ⒸIV
# First for Panic

**XANAX® Tablets**
**(alprazolam, ⒸIV Upjohn)**

### INDICATIONS AND USAGE

Generalized anxiety disorder, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life does not usually require an anxiolytic.

Panic disorder, with or without agoraphobia.

Effectiveness has been established for up to 4 months for anxiety disorder and 4 to 10 weeks for panic disorder; but panic disorder has been treated open label for up to 8 months with no apparent loss of benefit. The usefulness should be reassessed periodically.

### CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow-angle glaucoma.

### WARNINGS

***Dependence and withdrawal reactions, including seizures***

Physical dependence on XANAX can produce certain adverse clinical events, some life-threatening. These include a spectrum of withdrawal symptoms—the most important is seizure. Even after relatively short-term use at 0.75 to 4 mg per day, there is some risk of dependence; but the risk and severity seem to be greater in patients treated with doses above 4 mg/day for more than 8 to 12 weeks.

***Treatment of panic disorder: Dose and risks of XANAX***

Panic-disorder patients often need doses greater than 4 mg/day, hence the risk of dependence may be greater than in patients treated for less severe anxiety. Based on studies involving 641 patients, the most frequent symptoms seen during discontinuation were:

***Neurologic:*** Insomnia, light-headedness, abnormal involuntary movement, headache, muscular twitching, impaired coordination, muscle-tone disorders, weakness.

***Psychiatric:*** Anxiety, fatigue and tiredness, irritability, cognitive disorder, memory impairment, depression, confusional state.

***Gastrointestinal:*** Nausea/vomiting, diarrhea, decreased salivation.

***Other systems:*** Weight loss, decreased appetite, sweating, tachycardia, blurred vision. It has not been determined if these symptoms are clearly related to dose and duration of therapy. In two controlled trials of the discontinuation of XANAX lasting 6 to 8 weeks, 71% to 93% of patients treated with XANAX compared with 89% to 96% of placebo patients tapered completely off medication. The ability of patients to completely discontinue after long-term therapy has not been reliably determined.

Seizures were reported in 8 of 1,980 patients who took more than 4 mg XANAX daily for over 3 months, generally during abrupt dose reduction. There have been occasional reports of seizures during gradual taper; the risk seems to be greatest 24 to 72 hours after discontinuation.

***Status epilepticus and its treatment:*** Discontinuation of XANAX has been associated with seizures. In most cases a single seizure was reported; however, multiple seizures and status epilepticus have been reported. Treatment is the same as that for status of any cause.

***Interdose symptoms:*** Early morning anxiety and emergence of anxiety symptoms between doses have been reported in panic patients taking XANAX. It can usually be managed with more frequent administration of the same total daily dose or by increasing total dosage.

***Risks of dose reduction:*** Withdrawal reactions may occur with dosage reduction for any reason; dosage should be reduced gradually. (See DOSAGE AND ADMINISTRATION.)

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. (See DRUG ABUSE AND DEPENDENCE and DOSAGE AND ADMINISTRATION.)

### PRECAUTIONS

***General:*** If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See DRUG INTERACTIONS.) Use the usual precautions in patients with impaired renal, hepatic, or pulmonary function and regarding prescription size in depressed and suicidal patients. Use the smallest effective dose to avoid ataxia or oversedation, which may be a particular problem in elderly or debilitated patients. Alprazolam plasma half-life may be prolonged in obese patients or those with alcoholic liver disease. There have been rare reports of death in patients with severe pulmonary disease shortly after the start of therapy with XANAX. Episodes of mania and hypomania have been reported in depressed patients. Alprazolam is weakly uricosuric.

***Information for patients:*** For all users of XANAX. Alert patients about: (1) consumption of alcohol and drugs, (2) not taking any benzodiazepine during pregnancy or while nursing, (3) operating machinery or driving, (4) not increasing the dose due to risk of dependence, (5) not stopping the drug abruptly.

Additional advice for panic patients:

Use of more than 4 mg per day of XANAX for long periods of time may cause severe emotional and physical dependence in some patients, and these patients may find it difficult to stop treatment. In two studies lasting 6 to 8 weeks, 7% to 29% of patients treated with XANAX did not completely taper off therapy. The ability of patients to completely discontinue therapy has not been determined. Also, extended use of high doses appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor, but seizure, which can be life-threatening, can occur, especially if dose is reduced too rapidly or stopped abruptly.

***Laboratory tests:*** Not ordinarily required in otherwise healthy patients.

***Drug interactions:*** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine and oral contraceptives can delay clearance of benzodiazepines. ***Drug/laboratory test interactions:*** No consistent pattern. ***Carcinogenesis, mutagenesis, impairment of fertility:*** No carcinogenic potential or impairment of fertility in rats. ***Pregnancy:*** See WARNINGS. ***Nonteratogenic effects:*** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity, and respiratory problems. ***Labor and delivery:*** No established use. ***Nursing mothers:*** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. ***Pediatric use:*** Safety and effectiveness in children below the age of 18 have not been established.

### ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or light-headedness.

***Central nervous system:*** Drowsiness, light-headedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. Impaired coordination, irritability, memory impairment, cognitive disorder, dysarthria, anxiety, abnormal involuntary movement, changed libido, muscular twitching, weakness, muscle-tone disorders, agitation, disinhibition, paresthesia, talkativeness, vasomotor disturbances, derealization, dream abnormalities, fear, feeling warm.

***Gastrointestinal:*** Dry mouth, constipation, diarrhea, nausea/vomiting, increased salivation, decreased salivation, and abdominal distress.

***Cardiorespiratory:*** Tachycardia/palpitations, hypotension, nasal congestion, chest pain, hyperventilation, upper respiratory infection.

***Other:*** Blurred vision, rigidity and tremor, tinnitus, muscular stiffness and cramps, sweating, skin disorders, rash, change in appetite, micturition difficulties, menstrual disorders, sexual dysfunction, edema, incontinence, infection, dermatitis/allergy, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See WARNINGS.)

To discontinue treatment, dosage must be reduced slowly by no more than 0.5 mg every 3 days.

The following adverse events have been reported with benzodiazepines: dystonia, concentration difficulties, anorexia, slurred speech, jaundice, pruritus, diplopia.

Untreated panic disorder has been associated with depressive disorders and suicide. When treating panic patients, the same caution must be used as in treating patients with depression or suicidal ideation.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia, and galactorrhea have been reported; but no causal relationship was established.

### DRUG ABUSE AND DEPENDENCE

***Physical and psychologic dependence:*** Withdrawal symptoms like those noted with sedative/hypnotics and alcohol have been seen after discontinuance of benzodiazepines. Symptoms can range from mild dysphoria and insomnia to a major syndrome including abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The distinction between withdrawal symptoms and recurrence of illness is difficult. Withdrawal typically includes new symptoms, occurs toward the end of taper or shortly after discontinuation, and decreases with time. Recurrent panic disorder recurs early or late, with persistent symptoms similar to the initial presentation. When necessary XANAX should be restarted in adequate dosage.

Withdrawal symptoms, including seizures, may occur after brief therapy with dosages of 0.75 to 4 mg/day, but severity and incidence are apparently increased after dosages above 4 mg/day, after rapid decrease of dosage or abrupt discontinuation. Dosage should be gradually tapered under close supervision, especially in patients with a history of seizures or epilepsy.

Psychologic dependence is a risk with all benzodiazepines, increasing at higher doses, with long-term use, and in patients with a history of alcohol or drug abuse. Addiction-prone patients should be closely supervised when receiving XANAX and repeat prescriptions limited.

***Controlled Substance Class:*** XANAX is a controlled substance and has been assigned to schedule IV.

### OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported with overdosage of benzodiazepines by themselves or in combination with overdosage of alcohol.

### DOSAGE AND ADMINISTRATION

Dosage should be individualized, using the lowest effective dose. The need for treatment should be reassessed frequently.

Anxiety: The usual starting dosage is 0.25 to 0.5 mg t.i.d. Maximum daily dose is 4 mg. Patients who are elderly or debilitated, or have advanced liver disease, may be especially sensitive to benzodiazepines, and the starting dosage is 0.25 mg b.i.d. or t.i.d. Reduce dosage gradually, by no more than 0.5 mg every 3 days, or more slowly.

Panic disorder: Many patients required more than 4 mg daily. Mean dosage in studies was 5 to 6 mg/day, with a maximum of 10 mg/day. Treatment may be initiated with 0.5 mg t.i.d. Depending on the response, dosage may be increased every 3 or 4 days by up to 1 mg daily. After extended freedom from attacks, dosage should be carefully tapered by, at most, 0.5 mg every 3 days. Some patients may be resistant to all discontinuation regimens.

### HOW SUPPLIED

XANAX Tablets are available as 0.25-mg, 0.5-mg, 1-mg, and 2-mg tablets.

**CAUTION:** FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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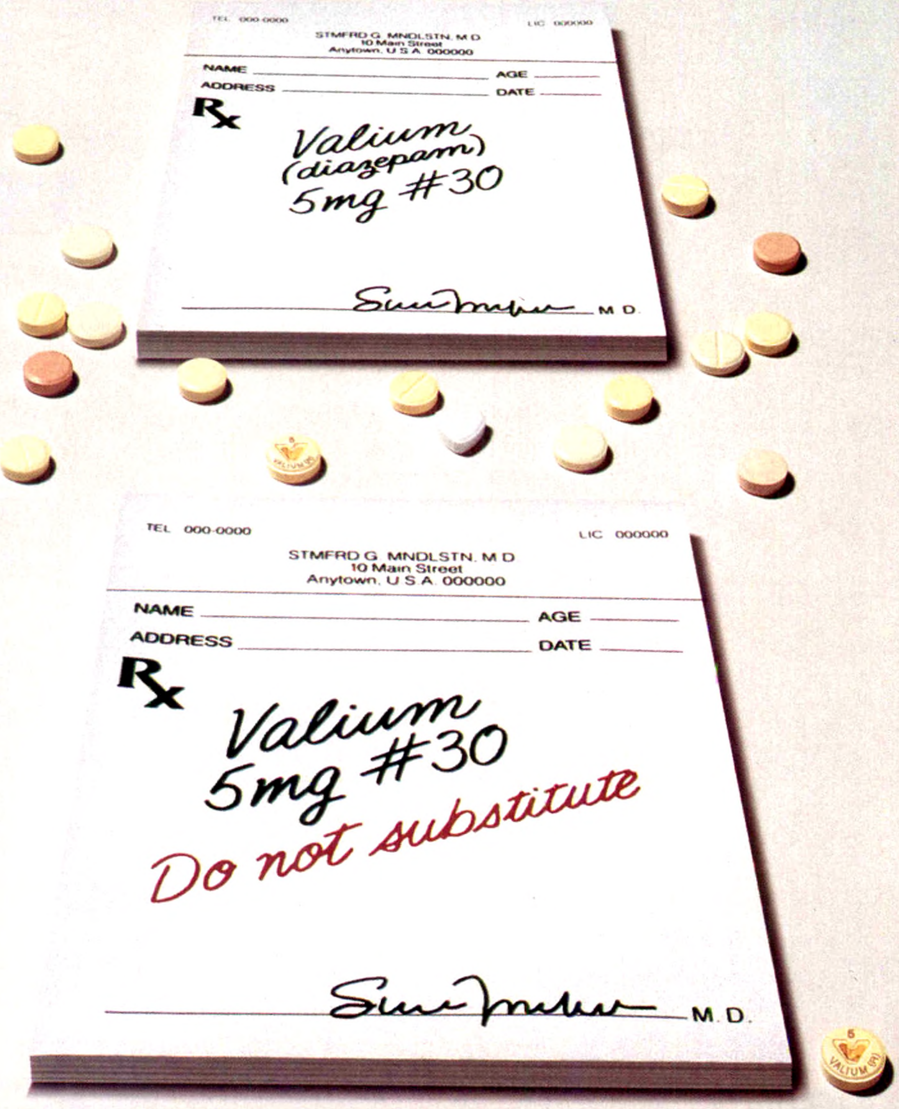

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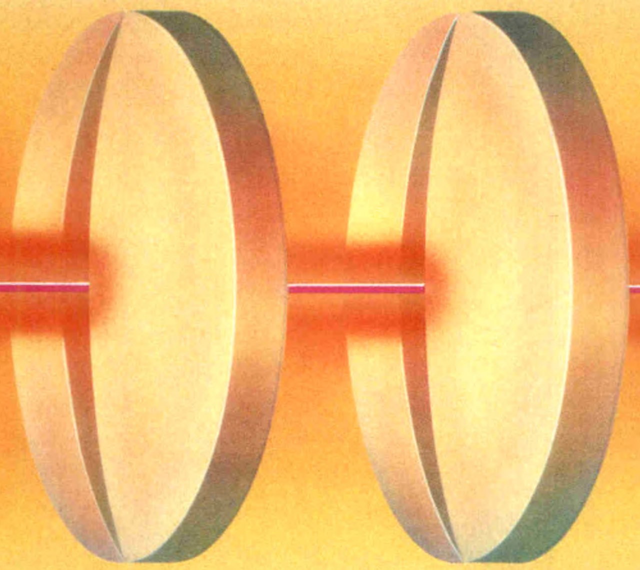

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* Appleton, Wm. S.: Treatment for Mood Disorders, Ch. 4, *Practical Clinical Psychopharmacology* (3rd Ed.), 132-135, 1988.
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**WARNING**

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see DOSAGE AND ADMINISTRATION in the complete prescribing information).

**Indications**
Treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

**Warnings**
Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion.

Chronic lithium therapy may be associated with diminution of renal concentrating ability. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. Caution patients about activities requiring alertness.

Lithium may prolong the effects of neuromuscular blocking agents. Such agents should be given with caution to patients receiving lithium.

Lithium carbonate may cause fetal harm when administered to a pregnant woman. If a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances.

Not recommended in children under 12.

Elderly patients often require lower lithium dosages to achieve therapeutic serum levels. They may also exhibit adverse reactions at serum levels ordinarily tolerated by younger patients

**Precautions**
Caution should be used when lithium and diuretics are used concomitantly. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary.

Sweating, diarrhea and concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Indomethacin and piroxicam have been reported to increase significantly, steady state plasma lithium levels. There is also some evidence that other nonsteroidal anti-inflammatory agents may have a similar effect. When such combinations are used, increased plasma lithium level monitoring is recommended. Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Monitor patients receiving such combined therapy closely.

**Adverse Reactions**
Adverse reactions may be encountered at serum lithium levels below 1.5 mEq./l. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq./l., and moderate to severe reactions may be seen at levels of 2.0 mEq./l. and above. Fine hand tremor, polyuria, and mild thirst may occur during initial therapy and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during initial therapy. These side effects usually subside with continued treatment or a temporary reduction or cessation of dosage. Diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq./l. At higher levels, ataxia, giddiness, tinnitus, blurred vision, and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq./l. may produce a complex clinical picture, involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq./l. during the acute treatment phase.

The following reactions appear to be related to serum lithium levels, including levels within the therapeutic range. *Neuromuscular/Central Nervous System*—tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreo-athetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes; *Cardiovascular*—cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; *Genitourinary*—glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst, and polydipsia; *Dermatologic*—drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema; *Autonomic*—blurred vision, dry mouth, impotence/sexual dysfunction; *Thyroid Abnormalities*—euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower $T_3$ and $T_4$. $I^{131}$uptake may be elevated. (See Precautions.) Paradoxically, rare cases of hyperthyroidism have been reported; *EEG Changes*—diffuse slowing, widening of the frequency spectrum, potentiation and disorganization of background rhythm; *EKG Changes*—reversible flattening, isoelectricity or inversion of T-waves; *Miscellaneous*—fatigue, lethargy, transient scotomata, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

**How Supplied**
Capsules contained 300 mg. lithium carbonate per capsule, in bottles of 100 and 500.

Tablets containing 300 mg. lithium carbonate per tablet, in bottles of 100.

Controlled Release Tablets containing 450 mg. lithium carbonate per tablet, in bottles of 100.

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# Books Received

**The Encyclopedia of Adoption,** by Christine Adamec and William L. Pierce, Ph.D. New York, Facts on File, 1991, 372 pp., $45.00.

**Words I Never Thought to Speak: Stories of Life in the Wake of Suicide,** by Victoria Alexander. New York, Lexington Books (Macmillan), 1991, 238 pp., $22.95.

**A Sacred Unity: Further Steps to an Ecology of Mind,** by Gregory Bateson. San Francisco, HarperCollins, 1991, 336 pp., $24.95.

**Cholinergic Basis for Alzheimer Therapy,** edited by Robert Becker and Ezio Giacobini. Boston, Birkhäuser, 1991, 490 pp., $64.50.

**Mind and Common Sense: Philosophical Essays on Commonsense Psychology,** edited by Radu J. Bogdan. Cambridge, Cambridge University Press, 1991, 206 pp., $44.50.

**HIV Counselling: Report on the National Survey and Consultation, 2nd ed.,** by Tim Bond. Barton, Cambridge, England, Daniels, 1992, 150 pp., £17.95 (paper).

**The Development of Intentional Action: Cognitive, Motivational, and Interactive Processes. Contributions to Human Development, vol. 22,** edited by Merry Bullock; Deanna Kuhn, series editor. Basel, Karger, 1991, 77 pp., $59.25.

**Psychiatric Words and Phrases,** by Mary Ann D'Onofrio and Elizabeth D'Onofrio. Modesto, Calif., Health Professions Institute, 1990, 256 pp., $27.00 (paper).

**Eros and Evolution: Prospects for PASO,** by Robert Endleman, Ph.D. New York, Psyche Press, 1991, 206 pp., $32.00.

**What Is Schizophrenia?** edited by William F. Flack, Jr., Daniel R. Miller, and Morton Wiener. New York, Springer-Verlag, 1991, 261 pp., (no price listed).

**Missing Children: Rhetoric and Reality,** by Martin L. Forst and Martha-Elin Blomquist. New York, Lexington Books (Macmillan), 1991, 301 pp., $22.95.

**Mental Health Services in the United States and England: Struggling for Change,** edited by Vivian E. Fransen. Princeton, Robert Wood Johnson Foundation, 1991, 168 pp., no charge (paper).

**Women on Top: How Real Life Has Changed Women's Sexual Fantasies,** by Nancy Friday. New York, Simon & Schuster, 1991, 461 pp., $22.00.

**Health Insurance in Practice: International Variations in Financing, Benefits, and Problems,** by William A. Glaser. San Francisco, Jossey-Bass, 1991, 533 pp., $70.00.

**Depression: New Trends in Research and Treatment,** edited by Per Kragh-Sørensen, Annette Gherris, and Tom G. Bolwig. Copenhagen, Munksgaard, 1991, 196 pp., 200 DKK (paper).

**Dual Diagnosis in Substance Abuse,** edited by Mark S. Gold and Andrew E. Slaby. New York, Marcel Dekker, 1991, 336 pp., $89.75.

**The Psychiatric Drug Handbook,** by Barry H. Guze, M.D., Huan-Kwang Ferng, M.D., Martin P. Szuba, M.D., and Steven Richeimer, M.D. St. Louis, Mosby Year Book, 1991, 304 pp., (no price listed).

**Mending Minds: A Guide to the New Psychiatry of Depression, Anxiety, and Other Serious Mental Disorders,** by Leonard L. Heston, M.D. New York, WH Freeman, 1992, 225 pp., $24.95;$13.95 (paper).

**Die Entwicklung depressiver Reaktionen in Kindheit und Jugend,** by Volker Hofmann. Berlin, Max-Planck-Institute für Bildungsforschung, (Rainer Bohn Verlag, distributor), 1991, 198 pp., DM 39,00.

**Psychopathologie cognitive,** edited by G. Loas, P. Boyer, and B. Samuel-Lajeunesse. Paris, Masson, 1991, 173 pp., 160 francs.

**Psychotropic Drugs: Fast Facts,** by Jerrold S. Maxmen. New York, WW Norton, 1991, 279 pp., $29.95 (spiral-bound).

**The Evolution of Consciousness: Of Darwin, Freud and Cranial Fire—The Origins of the Way We Think,** by Robert Ornstein. New York, Prentice Hall Press, 1991, 299 pp., $25.00.

**Strategies in Social Work Consultation: From Theory to Practice in the Mental Health Field,** by Dwight W. Rieman. New York, Longman, 1992, 187 pp., $31.95.

**Sex in the Forbidden Zone: When Men in Power— Therapists, Doctors, Clergy, Teachers, and Others— Betray Women's Trust,** by Peter Rutter, M.D. New York, Fawcett Crest, 1989, 288 pp., $5.99 (paper).

**Before Their Time: Four Generations of Teenage Mothers,** by Joelle Sander. New York, Harcourt Brace Jovanovich, 1991, 190 pp., $19.95.

**Atlas of Sleep Medicine,** edited by John W. Shepard, Jr., M.D. Mount Kisco, N.Y., Futura, 1991, 279 pp., $150.00.

**Mind and Society: Structural Thinking in Integral Psychiatry, Based on Longitudinal Observations,** by A. Sunier. Assen, The Netherlands, Van Gorcum, 1991, 180 pp., Fls. 47.50.

**Child Psychiatric Epidemiology: Concepts, Methods, and Findings,** by Frank C. Verhulst and Hans M. Koot. Newbury Park, Calif., Sage, 1992, 145 pp., $29.95; $13.95 (paper).

***n*-Hexane: Environmental Health Criteria 122,** by the World Health Organization. Geneva, WHO, 1991, 164 pp., $18.00 (paper).

**Assumptions About Human Nature: Implications for Researchers and Practitioners, 2nd ed.,** by Lawrence S. Wrightsman. Newbury Park, Calif., Sage, 1992, 350 pp., $29.95;$14.50 (paper).

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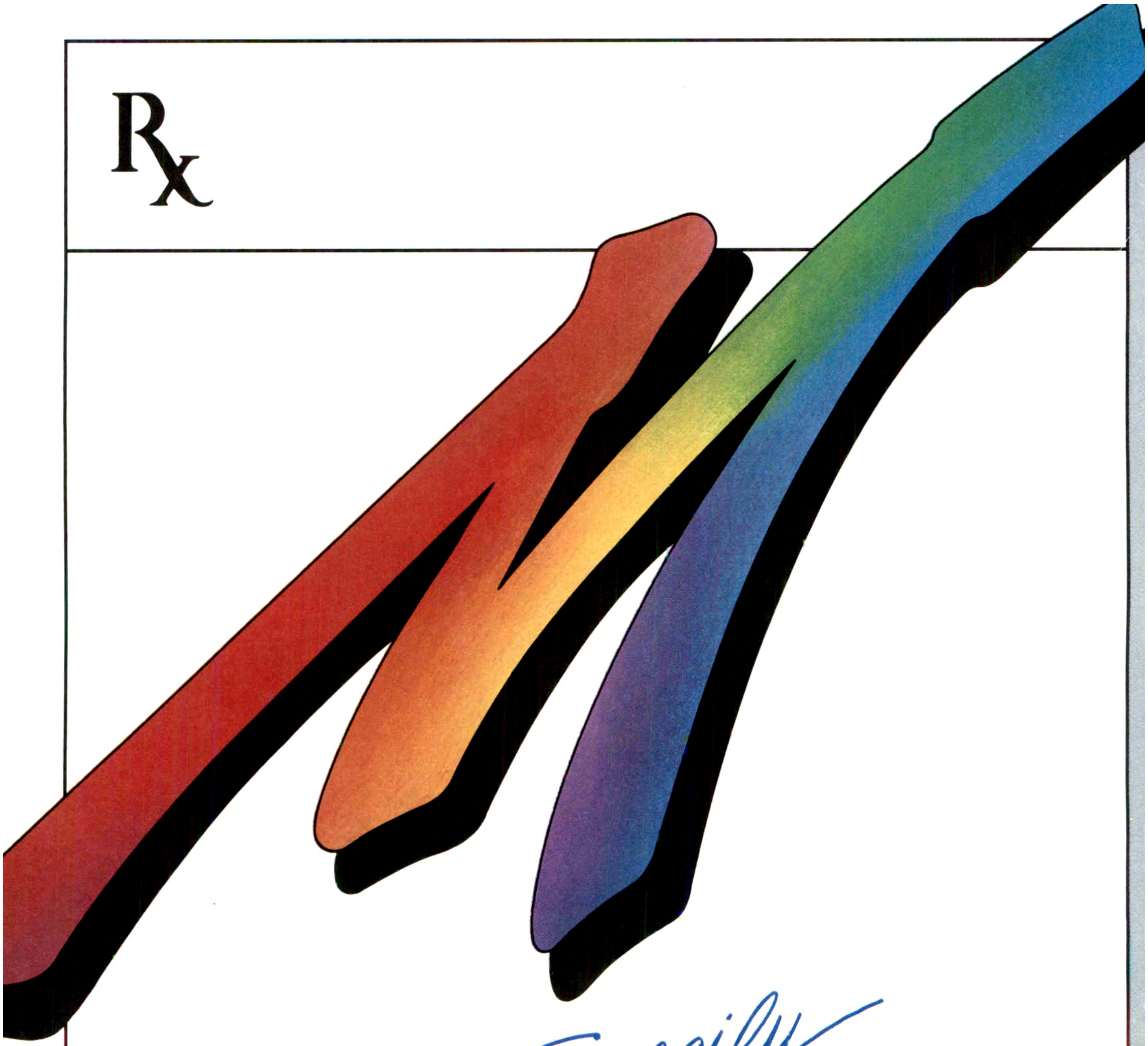

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# The Efficacy of Brief Dynamic Psychotherapy: A Meta-Analysis

**Paul Crits-Christoph, Ph.D.**

*Objective: Insurance companies, legislators, and funding agencies have become increasingly concerned with efficacy and accountability in regard to psychotherapy, and psychodynamic therapy is a primary target of concern because it is widely practiced in outpatient settings. This paper is a meta-analytic review of recent well-controlled studies of the efficacy of brief dynamic therapy. Method: The meta-analysis included both published studies, located through an extensive computerized search of psychiatry and psychology journals, and studies reported at conferences. Eleven studies met the inclusion criteria: use of a specific form of short-term dynamic psychotherapy as represented in a treatment manual or manual-like guide; comparison of brief dynamic therapy and a waiting list control condition, nonpsychiatric treatment, alternative psychotherapy, pharmacotherapy, or other form of dynamic therapy; provision of the information necessary for calculation of effect sizes; at least 12 therapy sessions; and therapists who were trained and experienced in brief dynamic therapy. The outcome measures compared were target symptoms, psychiatric symptoms generally, and social functioning. Results: Brief dynamic therapy demonstrated large effects relative to waiting list conditions but only slight superiority to nonpsychiatric treatments. Its effects were about equal to those of other psychotherapies and medication. Conclusions: These data confirm previous indications that various psychotherapies do not differ in effectiveness, although this finding should not be generalized to all patient populations, outcome measures, and treatment types. Also, the highly controlled conditions of these studies limit conclusions about actual practice. Future studies should address various treatment lengths, follow-up assessments, and specific treatments, patient groups, and outcome measures.*
(Am J Psychiatry 1992; 149:151–158)

Over the past decade, insurance companies, legislators, and funding agencies have become increasingly concerned with efficacy and accountability in regard to psychotherapy (1). Psychodynamic therapy, because it is widely practiced in outpatient settings, is a natural target for such concerns about efficacy. Although there have been a number of reviews of the literature on the efficacy of psychotherapy in general (2, 3) and the efficacy of specific treatments (4, 5), few reviews have been devoted to the efficacy of psychodynamic therapy in particular. An obvious reason for this is the relative dearth until recent years of well-controlled studies of the outcome of dynamic psychotherapy. In addition, a variety of methodological problems hindered the interpretation of results from earlier studies.

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Received Feb. 8, 1991; revision received June 17, 1991; accepted July 16, 1991. From the Department of Psychiatry, School of Medicine, University of Pennsylvania. Address reprint requests to Dr. Crits-Christoph, 301 Piersol Bldg., Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

Supported in part by NIMH Clinical Research Center grant MH-45178, grant MH-40472, and Career Development Award MH-00756 to Dr. Crits-Christoph.

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Perhaps the greatest problem with many efficacy studies of dynamic therapy has been the lack of control and specification of the treatment variable. The improvements in outcome research due to the use of treatment manuals and careful selection, supervision, and monitoring of therapists are relatively recent (6). Many otherwise well-controlled studies of the efficacy of dynamic therapy (e.g., 7–10) left unanswered questions about the meaning of the findings because the nature of the treatment provided by dynamic therapists was not clearly specified and controlled. These studies in general allowed dynamic therapists to conduct treatment as they usually practiced, on the assumption that differing orientations and styles among dynamic therapists are of little concern. Although such naturalistic treatment studies perhaps generalize better to the eclectic practice of dynamic therapy as it actually occurs, recommendations about specific treatment approaches cannot be based on such studies. In addition, recent evidence (11) indicates that studies which do not use treatment manuals are much more prone to therapist effects (i.e., significant differences between therapists in outcomes) than are studies which do use treatment manuals. Such therapist effects create a statistical problem of nonindependence, which can lead to highly distorted conclusions about the efficacy of treatments when ignored in the analysis of comparative outcome data (as is typically the case) (12). Thus, many of the findings from studies of dynamic therapy that did not use manuals are questionable on statistical grounds and do not provide clear clinical recommendations because of the eclectic treatment. Moreover, although the use of a dynamic therapy treatment manual does not necessarily lead to greater treatment benefits, the more careful selection, training, and monitoring of therapists in the recent comparative studies using manuals are likely to provide the highest quality of treatment possible.

In the area of brief dynamic therapy, a number of specific dynamic approaches have now been articulated in the form of guides or manuals to be used in the training of therapists: Luborsky (13), Strupp and Binder (14), Sifneos (15), Davanloo (16), Mann (17), Horowitz (18), and others. Although not all of these books have been labeled "manuals," what they have in common are a clearly laid out theory, detailed case examples, and a set of technical recommendations for the practice of a *particular* dynamic therapy (19). In addition, these guides lend themselves well to use in a research context, and studies implementing these approaches are beginning to accumulate.

Because of these improvements in outcome research, I was able to conduct a meta-analytic review (20) of the evidence for the efficacy of short-term dynamic therapy, attending only to studies that controlled the treatment variable through the use of a manual or manual-like guide for therapists. Three main questions were addressed: 1) To what extent is there evidence that brief dynamic therapy is more effective than no treatment? 2) How does brief dynamic therapy compare to regular contact with patients that is not standard psychiatric treatment? and 3) How does brief dynamic therapy compare to other forms of psychiatric treatment, including medication and nondynamic psychotherapies? In addition to summarizing the literature on these questions, I will make recommendations about future research that would advance this area of study.

## METHOD

### *Selection of Studies*

To qualify for this review, a study had to test the efficacy of a specific form of short-term dynamic therapy as represented in a treatment manual or manual-like guide. Studies comparing brief dynamic therapy to a waiting list control condition, a nonpsychiatric treatment, an alternative psychotherapy, pharmacotherapy, or another form of dynamic therapy (or some combination of these comparison conditions) were included. In addition, only reports that included the information necessary for the calculation of effect sizes (discussed later) were included. The review was not restricted to published studies but included studies that had been presented at conferences. The published studies were found through an extensive computerized search of psychiatry and psychology journals.

Any study that did not involve a patient group (e.g., analogue study) was excluded from the review. The shortest study accepted for the review was the 12-session treatment described by Mann (17). Also excluded from the review were studies that used therapists who were not specifically trained and experienced in brief dynamic therapy techniques. This excluded studies which either used trainees or used experienced therapists who had not received training in short-term dynamic therapy. This criterion was chosen because most therapists with a psychodynamic orientation tend to adhere to long-term treatment and are slow to adapt to the philosophy of short-term therapies (21).

The 11 studies that met the inclusion criteria are listed in table 1 with the type of patients, treatment conditions, number of patients in each condition, and length of therapy for each study. These studies included tests of the efficacy of the brief dynamic treatments described by Mann (17), Davanloo (16), Luborsky (13), Horowitz (18), Pollack and Horner (32), Strupp and Binder (14), Malan (33), and Klerman, Weissman, Rounsaville, and Chevron (34). The interpersonal approach of Klerman et al., although less like other dynamic therapies in that the relationship with the therapist is not generally a focus of intervention, was included because of its historical roots in the work of Sullivan. In addition, the NIMH Treatment of Depression Collaborative Research Program (35) identified the interpersonal approach as generally within the psychodynamic domain, and psychodynamically oriented therapists were selected to perform the treatment in that study.

The 11 studies typically had a training period for

**TABLE 1. Studies of the Efficacy of Brief Dynamic Psychotherapy**

| Authors | Disorder | Treatment Conditions | N | Treatment Length |
|---|---|---|---|---|
| Piper et al. (22) | Mixed | Dynamic | 48 | Mean=18.6 sessions |
|  |  | Waiting list | 57 | 5 months |
| Shefler and Dasberg (unpublished, 1989) | Mixed | Dynamic | 16 | Mean=12 sessions |
|  |  | Waiting list | 17 | 3 months |
| Elkin et al. (23) | Depression | Interpersonal | 47 | Mean=16.2 sessions[a] |
|  |  | Cognitive | 37 | Mean=16.2 sessions[a] |
|  |  | Imipramine | 37 | Mean=16.2 sessions[a] |
|  |  | Placebo and clinical management | 35 | Mean=16.2 sessions[a] |
| Rounsaville et al. (24) | Opiate addiction | Interpersonal | 22 | Mean=13.2 |
|  |  | Low-contact | 28 | 1 session/month for 6 months[b] |
| Winston et al. (25) | Personality disorders | Dynamic—Davanloo | 15 | ≤40 sessions |
|  |  | Dynamic—Pollack and Horner | 17 | ≤40 sessions |
|  |  | Waiting list | 17 | 5 months |
| Thompson et al. (26) | Depression | Dynamic | 30 | 16–20 sessions |
|  |  | Cognitive | 31 | 16–20 sessions |
|  |  | Behavioral | 30 | 16–20 sessions |
| Brom et al. (27) | Posttraumatic stress disorder | Dynamic | 29 | Mean=18.8 sessions |
|  |  | Desensitization | 31 | Mean=15 sessions |
|  |  | Hypnotherapy | 29 | Mean=14.4 sessions |
|  |  | Waiting list | 23 | 4 months |
| DiMascio et al. (28) | Depression | Interpersonal | 17 | Mean=16 sessions |
|  |  | Amitriptyline | 20 | Mean=16 sessions |
|  |  | Low-contact | 21 | ≤1 session/month |
| Carroll et al. (29) | Cocaine abuse | Interpersonal | 21 | ≤12 sessions |
|  |  | Relapse prevention | 21 | ≤12 sessions |
| Woody et al. (30) | Opiate addiction | Dynamic | 32 | Mean=12 sessions |
|  |  | Cognitive | 39 | Mean=9.5 sessions |
|  |  | Drug counseling | 35 | Mean=17 sessions |
| Marmar et al. (31) | Pathological grief | Dynamic | 31 | Mean=12 sessions |
|  |  | Self-help | 30 | Mean=12 sessions |

[a] Mean number of sessions for all patients who completed the study; data were not broken down by treatment group.

[b] Mean number of sessions not reported, but data on dropouts suggest low-contact patients attended a mean of approximately four sessions.

therapists before the actual outcome study, but, as indicated in the selection criteria, they did not use inexperienced therapists. On the contrary, most studies used highly experienced therapists. In four studies the average length of postgraduate clinical experience was more than 9 years. Four other studies listed only the minimum number of postgraduate years required for therapists who participated in the study (typically 2 years). One study used therapists who were not only experienced clinicians but also had supervised training in the particular form of brief dynamic therapy for 2 years before the start of the study. Another study employed therapists who had on the average 5.5 years of experience in working with the types of patients studied. One study did not specify the therapist experience level other than to say "an experienced psychiatrist."

### *Outcome Measures*

Rather than asking the broad question, Does brief dynamic therapy work? I asked three more specific questions: 1) Does short-term dynamic therapy affect the specific target symptoms or problem areas for which patients are seeking treatment? 2) Does short-term dynamic therapy change the general level of psychiatric symptoms, and 3) Does short-term dynamic therapy improve social functioning?

The goal of this meta-analytic review was, as much as possible, to assess the effects of brief dynamic therapy on specific outcome measures. Since different outcome measures may vary in their reliability and sensitivity to change (36), it has been recommended (37) that meta-analyses not combine information on different outcome measures. Although the practice of combining information on heterogeneous outcome measures was common in early meta-analyses (e.g., 2), more recent meta-analytic reviews (e.g., 5) have begun to focus on specific measures.

In selecting measures that could provide answers to my three questions, I had to chose measures that were available in most studies. To assess specific target symptoms or problem areas for which patients seek treatment, I examined two forms of outcome measures. For studies of heterogeneous patient groups, the target complaints method (38) was selected. This measure requires the patient to rate the severity of the three main problems for which he or she is seeking treatment. For studies that investigated dynamic therapy for a specific patient group (e.g., cocaine abusers), the main problem area was already defined by the nature of patient selection. In these studies, a measure of the severity of this particular problem area or disorder (e.g., the Beck Depression Inventory for depressed patients) was selected to represent change in target symptoms.

To answer the question about the effect of brief dynamic therapy on general levels of psychiatric symptoms, the SCL-90 (39) was chosen. The Social Adjustment Scale (40) was selected to assess social functioning. In each of

**TABLE 2. Effect Sizes for Comparisons of Brief Dynamic Psychotherapy and Other Treatment Conditions**

| Condition Compared With Brief Dynamic Psychotherapy | Number of Comparisons | Average Effect Size (d)[a] | | |
|---|---|---|---|---|
| | | Target Symptoms | General Psychiatric Symptoms | Social Adjustment |
| Waiting list control | 5 | 1.10 | 0.82 | 0.81 |
| Alternative nonpsychiatric treatments | 5 | 0.32 | 0.20 | 0.09 |
| Alternative psychiatric treatments | 9 | –0.05 | –0.01 | –0.05 |
| Other dynamic therapy | 1 | –0.25 | 0.05 | 0.04 |

[a] Calculated according to the method of Cohen (41).

the few cases where these measures were not discussed in the published version of the study, the original investigators were contacted and asked to provide data on the measure if it was used in the study. In two studies the Social Adjustment Scale was not used, but ratings on alternative measures of social functioning were available, and change on these other instruments was evaluated for this review. If no measure of the construct was available, no effect size was calculated.

In general, only assessments of outcome done at or near the termination of treatment were used for this review. Although it might be of interest to examine the effects of dynamic therapy some time after termination, since delayed effects might be expected, not enough reports of follow-up data are available yet.

### *Effect Size Calculations*

The primary defining characteristics of a meta-analysis are the calculation of effect sizes and the integration of these effect sizes across studies. For this study the calculation of effect sizes was guided by Cohen (41) and used his d statistic. Effect size was calculated as the posttreatment mean of the dynamic treatment group minus the posttreatment mean of the comparison group, divided by the standard deviation of the comparison group. In some cases, only the adjusted posttreatment means and standard deviations (adjusted for initial levels) were available, and these were used instead of the raw means. A pooled standard deviation (across treatment groups) was used when the standard deviation for the comparison group was not available.

Effect size calculated this way can be readily interpreted as the distance, in standard deviation units, that the average brief dynamic therapy patient was from the average comparison group patient. An effect size of zero indicates that the dynamic therapy and comparison groups were equal in outcome. All calculations were made so that a positive effect size indicates superiority of brief dynamic therapy and a negative effect size indicates superiority of the comparison condition. Thus, an effect size of 0.50 would indicate that the improvement of the average dynamic therapy patient was one-half of the standard deviation more than that of the average comparison group patient. Because the effect size is in units of standard deviations, it can be converted directly into a percentage representing nonoverlap of the distributions (41). For example, an effect size of 1.00 would indicate that the average dynamic therapy patient was better off than 84% of the comparison group patients.

As an aid in interpreting effect sizes, Cohen (41) provided benchmarks for his d statistic. A value of 0.2 represents a small effect for the behavioral sciences, 0.5 a medium effect, and 0.8 a large effect. I will present alternative views of the meaning of different effect sizes in the Conclusions section.

## RESULTS

Table 2 presents the effect sizes from the comparisons of brief dynamic therapy and the other conditions tested.

### *Waiting List*

Five comparisons, from four studies (22, 25, 27, Shefler and Dasberg), are included in the results shown in table 2. The effect size for target symptoms is especially large, has been reported in previous studies (e.g., 42), indicating that these measures are particularly sensitive to change.

When the effect sizes are translated into percentages, the data indicate that in terms of target symptoms the average brief dynamic therapy patient was better off than 86% of the waiting list patients. In terms of general symptoms (SCL-90), the average brief dynamic therapy patient was better off than 79% of the waiting list patients. For social adjustment, the average brief dynamic therapy patient was also better off than 79% of the waiting list patients.

### *Nonpsychiatric Treatments*

Five studies compared brief dynamic therapy to some form of comparison condition that was not a standard psychiatric treatment modality (i.e., not medication or an alternative psychotherapy). The expectation in all of these studies was that dynamic therapy would produce greater effects than the comparison conditions. These comparison conditions ranged from the placebo and clinical management condition of the NIMH Treatment of Depression Collaborative Research Program study (23) to standard drug counseling (30), mutual self-help groups (31), and two studies employing a low-contact treatment (24, 28).

Overall, the average effect sizes indicate little difference between the outcomes of brief dynamic therapy and these comparison conditions. The largest average effect was for target symptoms, indicating that the average dynamic therapy patient was better off than 62% of the comparison group patients. The average effects, however, may be misleading, as there is considerable variation among these studies, perhaps as a result of the various types of comparison conditions, patient groups, etc. The effect sizes were fairly large in two studies, i.e., a comparison of the effects of dynamic therapy and drug counseling (30) on general psychiatric symptoms (effect size=0.74) and a comparison of the effects of interpersonal therapy and low-contact therapy (28) on target symptoms (effect size=0.67). In addition, in three of the five studies there was a much higher dropout rate from the alternative treatment than from dynamic therapy.

### *Other Psychiatric Treatments*

Six studies (23, 26–30) yielded nine comparisons of brief dynamic therapy and other standard psychiatric treatments. The alternative treatments included medication and various cognitive and behavioral therapies. The predominant trend is clear: only small differences between brief dynamic therapy and other treatments are generally apparent. No individual study effect size was greater than 0.30.

The single comparison (25) of one form of dynamic therapy (Davanloo approach) with another (Pollack and Horner's brief adaptation therapy) yielded no evidence for the superiority of one treatment.

## CONCLUSIONS

### *Meaning of Effect Sizes*

The effect sizes shown by this analysis can be described as large according to Cohen's definition (41). The translation to percentages communicates even more directly the extent to which a patient is much better off receiving dynamic therapy than no treatment. These effects are somewhat larger than the effect size (0.68) presented by Smith and Glass (2) for the general effects of psychotherapy. The heterogeneous treatments and control conditions used by Smith and Glass, however, may account in part for this difference. Alternatively, it is possible that the more recent studies reviewed here, which controlled the delivery of treatment to a greater extent, demonstrated larger changes than did the naturalistic assessments of dynamic therapy in the past.

In addition to Cohen's definitions, the magnitude of the effects of dynamic therapy can be understood through comparison with other types of interventions in medicine. Rosenthal (43) has performed such comparisons using the Smith and Glass meta-analysis (2). He demonstrated that the 0.68 effect size found by Smith and Glass was larger than the effect sizes for several well-known clinical trials in medicine which were halted before completion because it was decided the effect was large enough that it would be unethical to withhold from some patients a clearly efficacious treatment. As mentioned, the effect sizes for dynamic therapy versus waiting list control conditions found here were even larger than the effect size reported by Smith and Glass.

Obviously, with aspects of patient care that involve death or serious illness, even a small treatment effect might be deemed to be especially important. Nevertheless, it is informative to see that the effects of brief dynamic therapy (and psychotherapies in general) are strong in comparison to the effects of such medical treatments.

Other forms of psychotherapy (besides dynamic) were not compared to waiting list control conditions in this investigation. Dobson (5) reported an average effect size of 2.15 (based on Beck Depression Inventory scores) for comparisons of Beck's cognitive therapy to a waiting list or no treatment for depression. Although this value is substantially larger than the effect sizes reported here for comparisons of brief dynamic therapy and waiting list conditions, there is as yet no direct evidence for superiority of cognitive therapy, because the two studies that directly compared a manual-based dynamic or interpersonal therapy to cognitive therapy for the treatment of depression (23, 26) showed no differences between these treatments. It is likely that depression is a condition that responds well to treatments and that this accounts for the large effect size reported by Dobson (5) for comparisons of cognitive therapy to a waiting list and to no treatment.

The data reported here on dynamic therapy's lack of superiority to other standard psychiatric treatments are perhaps not surprising in light of previous reviews of the psychotherapy literature which have shown that various treatments do not differ in their effectiveness (2, 3). The fact that these conclusions hold up in studies where the treatment variable has been standardized and controlled through the use of treatment manuals is, however, still noteworthy. Although this finding appears robust, it is probably unwarranted to generalize this conclusion across all patient populations, outcome measures, and treatment types. For example, brief dynamic therapy has yet to be compared with exposure and response prevention in the treatment of obsessive-compulsive disorder. It is conceivable that, given the documented success of this behavioral treatment, exposure and response prevention would be shown to be superior to dynamic therapy on measures of compulsive behaviors. In brief, these unresearched questions are still unanswered.

Despite the strong effects in the comparisons of brief dynamic therapy and waiting list control conditions, there was less evidence for brief dynamic therapy's superiority to other treatment conditions that were not standard psychiatric treatments. Some studies, however, did yield evidence of superior efficacy. Moreover, in several studies there were higher dropout rates with the alternative treatments than with dynamic therapy. However, given the variation in the findings and the diverse nature of the control conditions and patient groups, it is difficult to draw meaningful conclusions from this small set of studies. Clearly, more research is needed to assess whether brief dynamic therapy is more beneficial than drug counseling, self-help groups, and the like.

The rigorous requirements (such as careful selection, training, supervision, and monitoring of therapists and the use of treatment manuals) that have been implemented in psychotherapy outcome research and were used as criteria for selection of the studies reviewed here may limit the generalizability of the findings to the outpatient practice of dynamic therapy. On the one hand, the careful selection and supervision of therapists is likely to ensure that a high-quality service is delivered; on the other hand, therapists in practice are not bound by a particular treatment guide or manual. Therapists in practice would therefore have more flexibility in their clinical work, which could conceivably lead to more favorable outcomes. Thus, what is gained in knowledge about the use of specific treatments under controlled conditions might also be a loss in terms of generalizability to the actual current practice of dynamic psychotherapy. Not only were the studies reviewed here performed under highly controlled conditions, but some of the forms of treatment studied may not reflect dynamic therapy as it is typically practiced. Interpersonal therapy (34), for example, was investigated in four of the 11 studies, but this approach may be quite distant from the psychoanalytically oriented forms of dynamic therapy more commonly practiced. This aspect of the data base for this review further limits its generalizability.

### *What Is Missing?*

An examination of what is not contained in this review can help further illuminate its limitations and point the way for future research. Lack of information on certain treatments, patient groups, outcome measures, various treatment lengths, follow-up assessments, and interaction hypotheses will be discussed in turn.

Most notably missing from studies of brief dynamic therapy are evaluations of Sifneos's well-known approach (15). Although two studies comparing this approach to a waiting list control (44, 45) and a study involving Sifneos's approach and two other brief dynamic therapies (46) have been conducted, data from these studies were not presented in a manner amenable to a meta-analysis. Means and standard deviations (or significance tests) were not presented for these studies, and the types of outcome measures used here were not employed. In addition, two studies (44, 45) used trainees as therapists. These studies, however, are important contributions to the literature on brief dynamic therapy. Unlike many of the studies used for the meta-analysis reported here, these three studies of Sifneos's approach involved patients who were carefully selected on the basis of explicit criteria for short-term dynamic therapy. Also, the investigators in these studies attempted to operationalize psychodynamic change, rather than examining only symptomatic change. All three studies showed considerable positive evidence for the effectiveness of Sifneos's approach. More research is needed to document the size of the effect on different forms of outcome.

Another limitation of the studies I have reviewed is that many of the patient groups were types that clinicians believe are particularly difficult to treat. Included were two studies of opiate addicts (24, 30), one of cocaine abusers (29), and one of patients with personality disorders (25). Although brief dynamic therapy may be most indicated for adjustment disorders, some anxiety disorders, and relationship conflicts, studies focusing on these problems have not been performed, with the exception of one study on posttraumatic stress disorder (27). A larger effect size for brief dynamic therapy might be expected if these "ideal" patient types were chosen for research.

The outcome measures of target symptoms, general symptoms (SCL-90), and social adjustment (Social Adjustment Scale) were selected because these measures are commonly used and it is preferable to calculate effect sizes within outcome domains rather than combining results across domains and measures. These measures, however, do not capture the specific areas where short-term dynamic therapy theoretically should be most successful. Studies of more theoretically relevant measures—dynamic conflicts, transference themes, and relationship patterns (e.g., 47)—are beginning to appear, but these measures have not yet been used in efficacy studies. With the exception of Klerman's interpersonal therapy, which focuses on manifest social adjustment, the other brief dynamic therapies were evaluated in terms of outcome measures that were not the central focus of treatment. Therapies such as medication, cognitive therapy, and behavioral treatments, which do focus directly on overt symptoms, might be expected to achieve larger changes on these measures. Larger effects for brief dynamic therapy may be evident once theoretically relevant measures are studied. Although previous research has often failed to detect specificity of the effects of different treatments in theoretically important outcome domains, the lack of such findings is likely to be a function of the difficulty in measuring these domains.

In searching for changes in measures that are theoretically important for brief dynamic therapy, it is essential that patients receive an adequate "dose" of treatment. Howard et al. (48) pooled data from many studies of eclectic therapy to determine the relationship between "dose" of psychotherapy and symptomatic outcome. Their results indicated that 75% of patients achieve an effective "dose" of therapy (i.e., symptom relief) within 26 sessions. In psychodynamic therapy, important therapeutic work (the working through process) is likely to take place after the initial symptom relief, and an adequate period for such working through is probably necessary for dynamic change to occur. Thus, studies designed to test the efficacy of dynamic therapy should not only measure the theoretically important variables but should also allow enough time for change in these variables to occur.

It may not be necessary, of course, for the working through to occur only during psychotherapy sessions. A very brief (12-session) dynamic therapy might begin the working through, and then the successful patient might be able to continue the process after the termination of treatment (18). Research on this process would have to include assessment of therapeutic benefits some time after the treatment formally ends. As mentioned earlier, few follow-up results are available. Ideally, the follow-up period should be free of further treatment, since this additional treatment would confound interpretation of the benefits apparent at the follow-up assessment. No studies performed to date have attempted to control the follow-up period. With patients in need of further treatment, however, the ethical problems of withholding treatment would have to be considered.

A final issue not taken up by this review is the role of other factors that might moderate the relationship between treatment type and outcome. Investigators would do well to look for interactions between patient characteristics and treatment types in evaluating efficacy data. The study by Piper et al. (22) on changes associated with dynamic therapy and a waiting list control condition for patients with high and low "quality of object relations" is an excellent example of the examination of interactions. To a certain extent this issue reduces to the problem discussed earlier, defining the appropriate patient group for dynamic therapy. It is unlikely, however, that only patients who seem theoretically suitable for dynamic therapy will be selected in future studies, especially considering the current diagnostic emphasis in psychiatry and the resulting constraints on federally funded research. Rather than select patients on the basis of suitability for dynamic therapy, researchers are more likely to measure variations in patient characteristics and relate these variables to outcome within and across treatment modalities.

The construct of "suitability for dynamic therapy" itself needs further research. Although there are clinical indicators of this quality, no reliable and valid assessment device has yet been created that can be used to test these clinical hypotheses. Actually, it may be of interest to ask not only what types of patients are in general suitable for dynamic therapy but also what types of patients do best and worst in brief dynamic therapy compared to an alternative therapy. For example, when one compares the process of dynamic therapy and cognitive therapy, a hypothesis that comes to mind is that patients who have more interest in examining the subtle, complex meanings of events and interpersonal transactions are a better match (and therefore would have better outcomes) with dynamic therapy and that patients who are more task oriented and see things in a more cut-and-dried fashion would probably prefer a straightforward, logical therapy, such as cognitive therapy, which gives a clear, direct explanation of their problems and proceeds in steps with regular homework assignments. By asking these more and more refined questions, researchers stand a better chance of uncovering the conditions under which dynamic therapies and other therapies are most effective.

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# Is Sleep Deprivation Useful in the Treatment of Depression?

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*Objective: The authors critically reviewed the literature on clinical applications of sleep deprivation in the treatment of depression. Data Collection: They included all studies using sleep deprivation for clinical purposes, with the exception of treatment studies that did not provide follow-up beyond a night of recovery sleep. They focused on six uses of sleep deprivation: 1) to potentiate response to antidepressant medication (13 studies), 2) to hasten the onset of action of antidepressant medication or lithium (five studies), 3) to prevent recurrent mood cycles (four studies), 4) as an alternative to antidepressant medication (five studies), 5) as a diagnostic probe (two studies), and 6) to predict response to antidepressant medication (nine studies). Findings: Although the literature appears to demonstrate the efficacy of sleep deprivation as a potentiation strategy, these treatment studies have substantial methodological shortcomings. Well-designed pilot studies indicate that sleep deprivation may hasten the onset of action of thymoleptic medications. Sleep deprivation may prevent premenstrual mood swings, and response to sleep deprivation may differentiate depressive pseudodementia from primary degenerative dementia with depression. Studies attempting to use sleep deprivation to predict response to antidepressant medication have yielded inconsistent results. Conclusions: Given the noninvasive nature of sleep deprivation, it would be useful to determine if even a small subset of refractory patients respond to it. The authors suggest future research directions to determine the usefulness of this potential treatment.*

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Approximately 60 studies involving more than 1,700 patients (1) have described the antidepressant efficacy of sleep deprivation. The average response rate to a single night of sleep deprivation reported in such studies was nearly 60% (2). Sleep deprivation is an attractive antidepressant treatment because it acts rapidly and is noninvasive, inexpensive, and well tolerated by most patients. However, sleep deprivation usually precipitates only a transient antidepressant response. Wu and Bunney (1) reported that 83% of unmedicated patients and 59% of medicated patients relapsed after a night of recovery sleep. Furthermore, a patient's response to one night of sleep deprivation may not accurately predict his or her response to repeated treatments (3–7). Therefore, the clinical utility of sleep deprivation remains unclear.

Two articles (1, 2) have reviewed the phenomenology as well as possible underlying mechanisms of the response to sleep deprivation. However, these reviews did not focus on the clinical utility of sleep deprivation in the diagnosis and treatment of mood disorders. In this review, we will describe six possible clinical applications of sleep deprivation and discuss the published studies testing the efficacy of each application. Thus, we will summarize the current state of sleep deprivation research in terms of its relevance to patient care.

The possible clinical applications of sleep deprivation in mood disorders are listed in appendix 1. Four of these applications use sleep deprivation to treat depression, and the remaining two use response to sleep deprivation as a diagnostic aid or a prognostic tool. Since the relapse rate in unmedicated patients is high, the first three clinical applications use sleep deprivation in combination with antidepressant medication. In the first and most widely tested clinical application, sleep deprivation is used to potentiate a patient's response to antidepressant medication. Second, sleep deprivation has been combined with antidepressants or lithium at the beginning of treatment in an attempt to hasten the onset of action of the medication. Third, either alone or in combination with antidepressants, sleep deprivation may be useful in preventing recurrent mood cycles. Fourth, sleep deprivation alone has been used to treat unmedicated patients.

Thus, the first four clinical applications use sleep deprivation as an antidepressant treatment or as an adjunct to other thymoleptic treatments. The final two clinical

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**TABLE 1. Studies Using Sleep Deprivation to Potentiate Response to Antidepressant Medication**

| Author | Year | Type of Sleep Deprivation[a] | Number of Treatments | Duration of Follow-Up | Rating Scale |
|---|---|---|---|---|---|
| Zimanova and Vojtechovsky (8) | 1974 | Total | Not stated | 2–3 days | Von Zerssen scale |
| Bhanji and Roy (9) | 1975 | Total | Not stated | 14 days | Global self-assessment scale |
| Cole and Müller (10) | 1976 | Total | 1 or 2/week; mean=3.3 | "Weeks" | Hamilton scale |
| Sidorwicz (11) | 1976 | Total | Not stated | 7 days | Zung and Hamilton scales |
| Svendsen (12) | 1976 | Total | 1 or 2/week; mean=1.7 | 7 days | Cronholm-Ottoson scale |
| Laszlo (13) | 1977 | Total | 2/week; total≤14 | 14 days | Hamilton, Taylor, Beck scales |
| von Scheyen (14) | 1977 | Total | Mean=5 | 14 days | Hamilton scale |
| Wasik and Puchala (15) | 1978 | Total | 2/week; total≤8 | 30 days | Hamilton scale |
| Vovin et al. (16) | 1979 | Total | 2–3/week for 2–3 weeks, then 1/week; mean=3–8 | 3–12 months | Nuller scale |
| Waldmann et al. (17) | 1979 | Late partial | Mean>3 | 2–3 days | "SPES of Kühne" |
| Dessauer et al. (18) | 1985 | Late partial | 1/5 days; total=5 | 25 days | Bojanovsky-Chlovpkova and Luria scales |
| Nosachev (19) | 1985 | Total | 1 or 2/week; mean=6 | 3–6 months | Global self-assessment scale |
| Holsboer-Trachsler et al. (20, 21) | 1985,<br>1986 | Late partial | 3/week; total=3 | 10 days | Hamilton scale |
| Total | | | | | |

[a] In total sleep deprivation, patient stays awake for 36 hours; in late partial sleep deprivation, patient stays awake from 2:00 a.m. until 10:00 p.m.
[b] Decrease in score on rating scale.
[c] 32 of the patients were receiving medication.
[d] 72 of the patients were receiving medication.

applications attempt to use response to sleep deprivation as a diagnostic marker and a predictor of response to somatic treatments. For example, response to sleep deprivation has been used to differentiate dementia from depression in geriatric patients and to predict a patient's subsequent response to antidepressant medication in general or to a particular class of antidepressants.

A 1-day response to sleep deprivation is too transient to be clinically useful. Therefore, we included in our review only those treatment studies which included follow-up beyond a night of recovery sleep.

## USING SLEEP DEPRIVATION TO POTENTIATE RESPONSE TO ANTIDEPRESSANT MEDICATION

In 13 studies, chronically depressed patients receiving medication have been deprived of sleep in an attempt to improve their clinical status (table 1). The studies described in table 1 vary greatly in all aspects of their design, such as inclusion criteria, schedule of sleep deprivation treatments, duration of follow-up, and response criteria. These differences in design make comparisons across studies difficult.

Most of the investigators studied heterogeneous groups of depressed subjects. Thus, the study groups included patients with endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression. All of the studies listed in table 1 used adult patients; however, King et al. (22) described a 12-year-old boy receiving imipramine whose clinical status improved with the addition of sleep deprivation and lithium carbonate. None of the studies used standardized diagnostic interviews to classify patients. Dessauer et al. (18) were the only investigators who attempted to define a treatment-resistant sample on the basis of the number and duration of previous depressive episodes. No study examined treatment-resistant patients who were selected on the basis of number and type of previous antidepressant (or ECT) treatments. Although a number of investigators noted that their patients had not responded to previous trials of antidepressants, the nature and duration of these trials were not usually specified (9–11). In table 1 we included only those patients who were noted to be receiving "chronic" antidepressants, or, if the duration of treatment was specified, those patients who had been receiving medication for at least 3 weeks.

With three exceptions (17, 18, 20), these treatment potentiation studies used total sleep deprivation—keeping the patient awake for a 36-hour period. However, the frequency and total number of treatments varied from study to study and from patient to patient within the same study. In many studies, patients were treated with sleep deprivation once or twice a week until they responded or until a predetermined maximum number of treatments was reached. Using this approach in a

**TABLE 1 (continued)**

| Response Criterion[b] | Type of Depression | Number of Subjects | Responders | |
|---|---|---|---|---|
| | | | N | % |
| 28% | Endogenous | 20 | 3 | 15 |
| Not stated | Unipolar | 37[c] | 16 | 43 |
| | Bipolar | 2 | 1 | 50 |
| 30% | Unipolar | 8 | 7 | 88 |
| | Bipolar | 3 | 1 | 33 |
| | Secondary | 4 | 1 | 25 |
| Not stated | Endogenous (N=12), neurotic (N=5), unspecified (N=2) | 19 | 4 | 21 |
| Not stated | Unipolar, bipolar | 36 | 9 | 25 |
| Not stated | Endogenous | 14 | 9 | 64 |
| | Neurotic | 4 | 1 | 25 |
| | Periodic/cycloid | 6 | 4 | 67 |
| Not stated | Unipolar | 29 | 20 | 69 |
| Not stated | Endogenous | 27 | 10 | 37 |
| | Involutional | 7 | 3 | 43 |
| | Reactive | 4 | 2 | 50 |
| | Schizoaffective | 5 | 0 | 0 |
| | Neurotic | 5 | 0 | 0 |
| Not stated | Unipolar (N=23), bipolar (N=7) | 30 | 7 | 23 |
| Not stated | Mixed | 30 | 18 | 60 |
| Not stated | Treatment-resistant endogenous | 18 | 7 | 39 |
| 33% | Endogenous | 86[d] | 37 | 43 |
| 50% | Mixed | 17 | 10 | 59 |
| | | 411 | 170 | 41 |

sample of elderly patients, Cole and Müller (10) found that responders required a mean of 3.3 treatments, but von Scheyen's mixed-age sample (14) required a mean of five treatments. Some studies (8, 9, 11) did not specify the frequency or total number of treatments.

There is evidence (23–26) that partial sleep deprivation, where the patient is kept awake for only part of the night, may be as effective as total sleep deprivation. Specifically, late partial sleep deprivation, where the patient is awakened at about 2:00 a.m. and kept awake until 10:00 p.m., appears to be as effective as total sleep deprivation and more effective than early partial sleep deprivation. In early partial sleep deprivation, the patient is kept awake until 2:00 a.m., allowed to sleep from 2:00 a.m. to 7:00 a.m., and then kept awake until 10:00 p.m. Obviously, partial sleep deprivation produces less fatigue than total sleep deprivation and thus has advantages as a clinical intervention. Therefore, several groups have attempted to use late partial sleep deprivation to potentiate response to antidepressant medication. For example, Dessauer et al. (18) administered late partial sleep deprivation once every 5 days for a total of five treatments, and Holsboer-Trachsler et al. (20, 21) administered late partial sleep deprivation three times in a week. As can be seen in table 1, their response rates were comparable to those of the other studies.

However, it is difficult to compare response rates across studies, since the time point at which response was determined varied from 2 days (8, 17) to 3–12 months (16) after recovery sleep. Furthermore, each study used different outcome measures, and studies differed in the percent of improvement that was considered a clinical response. For example, Cole and Müller (10) required a 30% decrease in Hamilton Rating Scale for Depression score as a response criterion, but Holsboer-Trachsler et al. (20, 21) required a 50% decrease. Many of the studies specified the rating scale used but not the degree of change used to define a favorable response (9, 11–18). In all of the studies, both patients and raters were aware of the patient's sleep schedule and the purpose of the study.

The failure to use blind raters and to control for patient expectations are serious methodological shortcomings. Furthermore, only one study (18) included a comparison group. It is difficult to design a comparison or control group for sleep deprivation because patients must be aware of the fact that they are being deprived of sleep. This has been a major criticism of the sleep deprivation literature, and Milstein et al. (27) have argued that the reported response to sleep deprivation is in fact a placebo response. Dessauer et al. (18) created a comparison group by dividing patients into those with poor prognoses and those with good prognoses on the basis of the number and duration of their previous depressive episodes. Fourteen good-prognosis patients received medication alone, and 18 poor-prognosis patients received both medication and five late partial sleep deprivation treatments at 5-day intervals. At the end of 25 days, both groups had comparable outcomes. Dessauer et al. maintained that sleep deprivation was effective in potentiating the antidepressant medication because the outcome of the poor-prognosis group was better than expected, equaling that of the good-prognosis group. Of course, this conclusion can be challenged because neither patients nor raters were blind to the hypothesis of the study and because raters were aware of the patient assignments. Furthermore, the categorization of the poor-prognosis group may have been faulty, and it is unclear if their better-than-expected outcome was in fact due to the sleep deprivation.

Taken together, these studies represent a total of 411 patients whose antidepressant treatment was supplemented by sleep deprivation. Overall, the studies reported a response rate of 41%. Given the refractory nature of the patients' illnesses and the fact that sleep deprivation is a benign and simple procedure, this response rate can be viewed as encouraging. If one-third of treatment-resistant patients can be helped by adding sleep deprivation to their medication regimen, then sleep deprivation would certainly have an important role in the treatment of depressed patients. However, these studies can be criticized because of their methodological shortcomings. Therefore, although these initial results are promising, it is clear that the capacity of sleep deprivation to potentiate antidepressant medication warrants further study under more carefully controlled conditions.

**TABLE 2. Studies Using Sleep Deprivation to Hasten Onset of Action of Antidepressant Medication or Lithium**

| Author | Year | Treatment Group and Schedule[a] | Blind Raters | Duration of Study (days) | Result |
|---|---|---|---|---|---|
| Loosen et al. (28) | 1976 | Clomipramine plus total sleep deprivation (N=8): sleep deprivation on night 0, medication starts day 1<br>Clomipramine (N=8): medication starts day 1 | No | 10 | Clomipramine plus total sleep deprivation superior until day 10; significant difference on days 1–3 |
| Elsenga and van den Hoofdakker (29) | 1980 | Clomipramine plus total sleep deprivation (N=9): medication starts day 1, sleep deprivation on nights 1, 3, 8, 10<br>Placebo plus total sleep deprivation (N=9): placebo starts day 1, sleep deprivation on nights 1, 3, 8, 10<br>Clomipramine (N=9): medication starts day 1 | Yes | 15 | Clomipramine plus total sleep deprivation superior over 15 days according to self-ratings but not blind ratings |
| van Bemmel and van den Hoofdakker (30) | 1981 | Clomipramine plus sleep deprivation I: medication starts day 1, total sleep deprivation on nights 1, 3, 8; 2 hours of sleep on night 4 and 5 hours of sleep on night 9<br>Clomipramine plus sleep deprivation II: medication starts day 1, total sleep deprivation on nights 1, 3, 8; 5 hours of sleep on night 4 and 2 hours of sleep on night 9 | No | 10 | Both groups had better response on days 5–10 than groups studied in 1982/1983 (31) |
| Elsenga and van den Hoofdakker (31) | 1982/ 1983 | Clomipramine plus total sleep deprivation (N=10): medication starts day 1, sleep deprivation on nights 1, 3, 8, 10<br>Placebo plus sleep deprivation (N=10): placebo starts day 1, sleep deprivation on nights 1, 3, 8, 10<br>Clomipramine (N=10): medication starts day 1 | Yes | 15 | Clomipramine plus sleep deprivation group had lowest Hamilton rating after 1 week |
| Baxter et al. (32) | 1986 | Lithium plus late partial sleep deprivation (N=4): medication starts day 1, partial sleep deprivation on nights 1, 2<br>Placebo plus late partial sleep deprivation (N=4): placebo starts day 1, partial sleep deprivation on nights 1, 2<br>Lithium (N=4): medication starts day 1 | Yes[b] | 5 | Lithium plus late partial sleep deprivation group had lowest Hamilton rating after 3 days of sleep deprivation |

[a] Night 0 follows day 0. In total sleep deprivation, patient stays awake for 36 hours; in late partial sleep deprivation, patient stays awake from 2:00 a.m. until 10:00 p.m.

[b] Medication was double-blind.

## USING SLEEP DEPRIVATION TO HASTEN THE ONSET OF ACTION OF ANTIDEPRESSANT MEDICATION OR LITHIUM

Five controlled studies have attempted to use sleep deprivation to hasten the onset of action of antidepressant medication or lithium during the initial phase of treatment (table 2). These studies can also be viewed as attempts to prolong the antidepressant effect of sleep deprivation by combining it with medication. In either case, the goal is to achieve a more rapid antidepressant response than occurs with the use of medication alone. Compared with the studies using sleep deprivation as a potentiation strategy, the patient samples in these studies were smaller. However, each study had one or more control groups, and several used blind raters.

In 1978, Philipp (26) suggested that concurrent use of antidepressant medication could prolong the effect of a night of sleep deprivation and presented uncontrolled data to support this contention. Loosen et al. (28) were the first to compare systematically a group of patients receiving medication (clomipramine) with a group receiving medication plus sleep deprivation. The group receiving medication plus sleep deprivation received total sleep deprivation the night before the first dose of medication. The sleep deprivation patients had a superior outcome for the first 10 days of treatment, although the difference was statistically significant only for the first 3 days. Although ratings were done by two independent raters, the investigators did not note whether the raters were aware of patient assignments.

Elsenga and van den Hoofdakker (29, 31) and van Bemmel and van den Hoofdakker (30) also published a series of studies combining sleep deprivation with clomipramine. In these studies, patients treated with clomipramine and sleep deprivation were compared with a group receiving sleep deprivation and placebo and with a group receiving clomipramine alone. Patients in the clomipramine/sleep deprivation group and in the placebo/sleep deprivation group underwent 2 nights of total sleep deprivation a week for 2 successive weeks. Patients in the clomipramine/sleep deprivation group started taking clomipramine the night before the first sleep deprivation. In the first of these studies (29), self-ratings, but not blind ratings, showed that clomipramine/sleep deprivation was superior over the experimental period of 15 days. In a later study (31), the clomipramine/sleep deprivation group had lower scores on the Hamilton depression scale than the other groups at the end of the first week. However, by the end of 15 days, the Hamilton depression scores of the clomipramine/sleep deprivation group and the clomipramine group were comparable. The pilot data of van Bemmel and van den Hoofdakker (30) indicated that the ratings of the clomipramine/sleep deprivation group were further improved by limiting patients' sleep to 2 or 5 hours on the night after total sleep deprivation.

Baxter et al. (32, 33) hypothesized that the mood-stabilizing properties of lithium might be useful in preventing relapse after recovery sleep. In a pilot study, they selected patients with unipolar and bipolar depression who had previously demonstrated a positive response to partial sleep deprivation. Patients were randomly assigned to treatment with late partial sleep deprivation and lithium, late partial sleep deprivation and placebo, or lithium alone. On day 1 of the study, patients in the lithium treatment groups were given a loading dose that was calculated to yield a serum lithium level of 1.0 meq/liter that day. Late partial sleep deprivation was carried out on days 1 and 2. On day 5, patients in the late partial sleep deprivation/lithium group had significantly lower Hamilton depression scores than patients in the other two groups. Five patients who were crossed over from the late partial sleep deprivation/lithium group or the late partial sleep deprivation/placebo group to the other pill had superior results in the late partial sleep deprivation/lithium condition. Throughout the study, raters were blind to medication but not to late partial sleep deprivation.

These studies indicate that several nights of total sleep deprivation or late partial sleep deprivation, administered early in the course of treatment with clomipramine or lithium, may yield a faster antidepressant response than drug treatment alone. If this application of sleep deprivation proves to be effective in larger samples of patients, it would have substantial clinical utility. For example, it may be possible to decrease the period during which a patient poses a high suicide risk or to shorten the inpatient stay of patients whose clinical status requires that they be hospitalized until antidepressant medication takes effect. Thus, like ECT, sleep deprivation may have a role in inducing more rapid remission than other available treatments. Although sleep deprivation is unlikely to have as dramatic or predictable effects as ECT, it is also a considerably more benign intervention. Therefore, this application of sleep deprivation clearly warrants further study using larger samples, control groups, and blind raters.

## USING SLEEP DEPRIVATION TO PREVENT RECURRENT MOOD CYCLES

Several groups have attempted to use sleep deprivation to prevent mood cycles in patients with rapid-cycling disorder. Papadimitriou and Christodoulou (34) reported nine drug-free patients with rapid-cycling disorder (five bipolar, four unipolar) who were placed on a regimen of weekly total sleep deprivation in an attempt to prevent their depressive cycles. All of the patients had undergone numerous unsuccessful trials of antidepressants, and some had received ECT. In five of the nine patients, prophylactic sleep deprivation appeared to result in fewer depressive episodes and more periods of euthymia than the patients experienced at baseline. However, since antidepressant medication can induce or exacerbate rapid cycling (35), it is possible that the reduction in the patients' cycling was caused by the discontinuation of antidepressant medication. Furthermore, since sleep deprivation has been reported to precipitate mania in some patients with bipolar disorder (8, 36–38), it is surprising that none of the patients of Papadimitriou and Christodoulou (34) became manic in response to the sleep deprivation.

Kjellman et al. (39) reported two drug-free patients with unipolar depression whose cycles were prevented by regular sleep deprivation. Lovett Doust and Christie (40) described a patient with bipolar disorder taking clomipramine, lithium carbonate, and methotrimeprazine who deprived herself of sleep when she began to feel depressed. The patient kept herself awake for 5 nights over a period of 9 months and had substantially less depression and hypomania during that period than she had had during the preceding 9 months. These anecdotal reports indicate that prophylactic sleep deprivation, either alone or in combination with medication, may be useful for some patients with rapid-cycling mood disorder. However, the risk of precipitating mania would appear to be substantial in this population (41).

Parry and Wehr (42) reported a pilot study using total sleep deprivation in 10 patients with premenstrual syndrome. The patients were admitted to the hospital for a night of total sleep deprivation when their Hamilton depression scores reached 10 during the premenstrual phase of their cycle. Eight of the 10 patients responded with a decrease of at least 5 points on the Hamilton depression scale. When five of the responders were then entered into a random-order crossover comparison of late partial sleep deprivation and early partial sleep deprivation, late partial sleep deprivation was shown to be the superior treatment. Sleep deprivation would be an appealing treatment for premenstrual syndrome—patients who were symptomatic for less than 10 days of the month could avoid having to take medication throughout their entire cycle. Therefore, a larger trial of sleep deprivation in premenstrual syndrome would be worthwhile.

## USING SLEEP DEPRIVATION AS AN ALTERNATIVE TO ANTIDEPRESSANT MEDICATION

Although 60% of drug-free patients had an antidepressant response to a night of sleep deprivation, 83% of them relapsed after a night of recovery sleep (1). Therefore, it is unclear whether sleep deprivation alone would be a viable treatment for acutely depressed patients. In a study providing unusually lengthy follow-up, Kvist and Kirkegaard (43) used 2 or 3 nights of total sleep deprivation as the only treatment in 28 patients with endogenous depression. Eight patients went into complete remission, but five of these responders relapsed within an average of 4 weeks. There was no comparison group, and raters were aware of the patients' sleep schedules.

Manthey et al. (44) treated six drug-free patients with late partial sleep deprivation twice a week for 3 weeks and noted a trend toward improvement. Papadimitriou and Christodoulou (34) treated 19 drug-free patients with total sleep deprivation twice a week for 4 weeks, followed by a maintenance program of weekly total sleep deprivation. Eight of the patients responded to the initial course, and four of the six patients who entered the prophylactic program were noted to have an "excellent response." However, the duration of the follow-up and the response criteria in this study were not clear. Uhde et al. (45) attempted to treat two drug-free bipolar disorder patients with sleep deprivation but found that its efficacy decreased with each successive treatment.

Vogel et al. (46) conducted a double-blind, crossover test of the hypothesis that 3 weeks of REM sleep deprivation would be an effective treatment for depression. Patients receiving REM sleep deprivation were awakened whenever they entered REM sleep, and patients in the control condition were awakened from non-REM sleep. Seventeen of 34 drug-free patients with endogenous depression responded to REM deprivation, and 14 of them stayed in remission for more than 6 months. Although Vogel's results are promising, REM sleep deprivation is a cumbersome procedure that requires continuous EEG monitoring. This has precluded replication of the experiment and would probably limit the clinical applicability of REM sleep deprivation.

The transient and unpredictable nature of the response to sleep deprivation means that sleep deprivation alone is unlikely to be an effective treatment for many depressed patients. However, patients who are unable to tolerate antidepressant medication, either because of side effects or medical contraindications, present the clinician with a difficult challenge. An initial course of sleep deprivation, followed by weekly maintenance treatment, may be a viable treatment option for some of these patients. However, the efficacy of sleep deprivation alone has not been tested in patients who are either treatment refractory or unable to tolerate medication.

## USING SLEEP DEPRIVATION AS A DIAGNOSTIC AID

When an elderly patient has depressive symptoms and cognitive impairment, the clinician may be hard pressed to distinguish depressive pseudodementia from primary degenerative dementia with depression. It is important to differentiate the two disorders because they have different treatments and prognoses. In 1986, Letemendia et al. (47) reported four depressed, confused patients who responded to a night of total sleep deprivation. While the patients were in the euthymic state induced by total sleep deprivation, their cognitive function was assessed and the diagnosis of dementia was ruled out.

In a related study, Buysse et al. (48) tested whether a positive response to sleep deprivation had diagnostic value in patients with symptoms of both depression and dementia. They found that a positive response to sleep deprivation distinguished patients with depressive pseudodementia from those with primary degenerative dementia with depression in a study group of 26 patients. Given the high prevalence of both organic and depressive symptoms in the elderly and the noninvasive nature of sleep deprivation, this application could have substantial clinical utility.

## USING SLEEP DEPRIVATION TO PREDICT RESPONSE TO ANTIDEPRESSANT MEDICATION OR ECT

In 1976, Wirz-Justice et al. (49) suggested that patients who felt less depressed the morning after sleep deprivation (day-1 responders) were likely to respond to an antidepressant that inhibits serotonin uptake, such as clomipramine. In addition, they suggested that patients who felt less depressed on the day after recovery sleep (day-2 responders), who represent 10% of the responders to sleep deprivation, would respond preferentially to an antidepressant that inhibits noradrenergic uptake, such as maprotiline. Wirz-Justice et al. presented pilot data from an open study to support this hypothesis (table 3).

Eight other studies have also addressed the question of whether response to sleep deprivation can predict response to antidepressant medication in general or to a particular class of antidepressants (table 3). In a follow-up to their original report, Wirz-Justice et al. (52) found that a response to total sleep deprivation on day 1 or day 2 predicted a good response to antidepressants in general, although total sleep deprivation response did not predict response to a particular class of antidepressants. In contrast, both Höchli et al. (54) and Reimann and Berger (55) found that a positive response to total sleep deprivation response predicted a negative response to clomipramine, and Amin (50) reported that total sleep deprivation response had no predictive value. Further complicating the situation, Fahndrich (53) studied a relatively large sample of patients and concluded that a positive response to total sleep deprivation predicted a positive response to clomipramine and a negative response to total sleep deprivation predicted a positive response to maprotiline.

The open design of these studies may account for their contradictory results. Two other studies have used a double-blind design to study the prognostic value of sleep deprivation. Roy-Byrne et al. (4) reported that a positive response to total sleep deprivation predicted a positive response to carbamazepine, and Kasper et al. (56), in a double-blind study confirming the original report of Wirz-Justice et al. (49), found that day-2 re-

TABLE 3. Studies Using Sleep Deprivation to Predict Response to Antidepressant Medication

| Author | Year | Number of Subjects | Medication | Duration of Treatment (days) | Rating Scale | Response Criterion | Result |
|---|---|---|---|---|---|---|---|
| Wirz-Justice et al. (49) | 1976 | Not stated | Clomipramine, maprotiline | Not stated | Not stated | Not stated | Positive day-1 response to total sleep deprivation[a] predicted positive clomipramine response; positive day-2 response to total sleep deprivation predicted positive response to maprotiline |
| Amin (50) | 1978 | 22 | Maprotiline, viloxazine, imipramine | 28 | Hamilton scale | 30% decrease in score | Total sleep deprivation had no predictive value |
| Philipp and Werner (51) | 1979 | 15 | Lofepramine | 21 | Hamilton scale | 35% decrease in score | Positive response to late partial sleep deprivation[b] predicted positive response to lofepramine |
| Wirz-Justice et al. (52) | 1979 | 52 | Maprotiline, clomipramine, imipramine | Not stated | Hamilton scale | 33% decrease in score for sleep deprivation, hospital discharge for drug response | Positive response to total sleep deprivation predicted positive general but not specific drug response |
| Fahndrich (53) | 1983 | 60 | Intravenous clomipramine, intravenous maprotiline | 21 | Global self-assessment, Hamilton scale | Positive change in global score for sleep deprivation, 50% decrease in Hamilton score for drug response | Positive response to total sleep deprivation predicted positive response to clomipramine; negative response to total sleep deprivation predicted positive response to maprotiline |
| Roy-Byrne et al. (4)[c] | 1984 | 16 | Carbamazepine | 28–63 | Bunney-Hamburg scale | 2-point decrease in score | Positive response to total sleep deprivation predicted positive response to carbamazepine |
| Höchli et al. (54) | 1986 | 10 | Clomipramine | 18 | Hamilton scale, adjective checklist | 30% decrease in score | Positive response to total sleep deprivation predicted negative response to clomipramine |
| Riemann and Berger (55) | 1990 | 17 | Clomipramine | 19 | Hamilton scale | 30% decrease in score | Positive response to total sleep deprivation predicted negative response to clomipramine |
| Kasper et al. (56)[c] | 1990 | 42 | Fluvoxamine, maprotiline | 28 | Hamilton scale | 30% decrease in score | Positive day-2 response to total sleep deprivation predicted positive response to maprotiline |

[a] In total sleep deprivation, patient stays awake for 36 hours.
[b] In late partial sleep deprivation, patient stays awake from 2:00 a.m. until 10:00 p.m.
[c] Double-blind study.

sponders were more likely to respond to maprotiline than to the serotonin uptake inhibitor fluvoxamine.

It is conceivable that more double-blind studies would yield consistent results concerning the utility of total sleep deprivation as a predictor of response to antidepressant treatment. However, given their contradictory results, the existing studies do not clearly indicate a role for sleep deprivation in the prediction of antidepressant response.

## CONCLUSIONS

Depressed patients, who frequently complain of insomnia, react with surprise to the notion that staying awake at night may be a useful treatment for their depression. Clinicians, too, often respond with skepticism to the idea of using sleep deprivation as an antidepressant. This skepticism is well-founded, given the fact that the sleep deprivation literature is largely uncontrolled. Furthermore, the transient and somewhat unpredictable nature of the response to sleep deprivation makes it unlikely that it will be an effective treatment for the vast majority of unmedicated patients. However, our review indicates that several clinical applications of sleep deprivation bear further study under controlled conditions.

There is evidence from uncontrolled studies that sleep deprivation can potentiate the medication response of patients who have achieved a partial remission. Even well-controlled studies may be unable to demonstrate an overall effect in a sample of treatment-refractory patients because such a sample is likely to consist of a heterogeneous group of depressed patients. However, given the noninvasive nature of sleep deprivation, it would be useful to determine if even a small subset of refractory patients respond to sleep deprivation. If this responsive subset exists, and if the response lasts for approximately a week, then weekly sleep deprivation could be a useful adjunct to ongoing pharmacotherapy for some patients.

To define a subgroup of sleep-sensitive depressed subjects, it is necessary to identify reliable predictors of response to sleep deprivation. Several variables, including age, sex, and diagnosis, do not appear to be correlated with response to sleep deprivation (57). However, two possible predictors of response to sleep deprivation have been described. First, the presence of diurnal variation may predict a positive response to sleep deprivation (58–60). Patients with typical diurnal variation experience a gradual improvement in mood as the day wears on, and van den Hoofdakker (61) has suggested that sleep deprivation acts as an antidepressant because it allows this natural remission to continue, uninterrupted by sleep. Second, high nocturnal minimum rectal temperature during sleep deprivation may be associated with a positive clinical response (62; unpublished data of T.A.W.). If future studies confirm the reliability of these predictors, it may become easier to identify those refractory patients who would benefit from a trial of adjunctive sleep deprivation.

Even if a given patient responds to a single night of sleep deprivation, his or her response to subsequent sleep deprivation trials is unclear. There are reports that patients who respond to sleep deprivation do not do so predictably from night to night (3–7). Roy-Byrne et al. (4) suggested that patients develop tolerance to sleep deprivation, and Pflug (5) presented preliminary data in support of this contention. However, the data of Elsenga and van den Hoofdakker (63) suggest that the concurrent use of antidepressant medication improves the consistency of the response to sleep deprivation. To date, there has been limited systematic study of the degree to which response to sleep deprivation is replicable. Clearly, such studies would have implications for the utility of sleep deprivation as an adjunct to medication.

In addition to its use as a potentiation strategy, other applications of sleep deprivation that may hold particular promise include its use in hastening the onset of action of antidepressants, in treating late luteal phase dysphoric disorder, and in differentiating depressive pseudodementia from primary degenerative dementia with depression. Preliminary studies in each of these areas have had encouraging results. These studies have included appropriate control groups, but the sample sizes have been small and the results have not yet been replicated at different centers.

Clinicians frequently question whether outpatient sleep deprivation is a practical treatment. Specifically, they wonder whether depressed patients will have sufficient motivation to spend all or part of a night awake, as prescribed. To overcome this problem, several treatment centers in Europe have established weekly sleep deprivation clinics for patients who have suboptimal medication responses. Patients who have difficulty depriving themselves of sleep at home attend the overnight sleep deprivation clinic and stay awake in the company of a nurse or technician and other patients (personal communication from S. Kasper). In a controlled trial that we are conducting, using sleep deprivation to potentiate antidepressant medication, patients are admitted to an inpatient unit the evening before sleep deprivation and discharged the following morning. Further clinical experience with sleep deprivation will clarify whether such supervised clinics or brief hospitalizations are necessary to deprive patients of sleep or whether patients can successfully deprive themselves at home.

Future research will determine whether, and in which clinical situations, sleep deprivation is a practical and effective antidepressant treatment. Furthermore, sleep deprivation research contributes to a general understanding of the pathogenesis and treatment of mood disorders, since sleep deprivation may share a mechanism of action with other, more commonly used antidepressant treatments. For example, both tricyclic antidepressants (64, 65) and monoamine oxidase inhibitors (66, 67) suppress REM sleep, and Vogel (68) has argued that this property accounts for their therapeutic efficacy. In addition, sleep deprivation appears to augment a nocturnal surge of thyrotropin (37, 69) and elevate $T_3$ levels (70, 71) in normal individuals as well as in patients with unipolar and bipolar depression. This finding suggests that a trial of sleep deprivation may be a form of thyroid potentiation where the thyroid hormone comes from an endogenous source. The rapidity of the response to sleep deprivation may provide a relatively accessible means of probing the neurobiology of antidepressant therapies. In this way, research concerning the efficacy and mechanism of sleep deprivation's antidepressant properties may yield not only new therapeutic techniques but also an increased understanding of the biological mechanisms underlying affective illnesses and their treatment.

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**APPENDIX 1. Clinical Applications of Sleep Deprivation in Mood Disorders**

1. Potentiate response to antidepressant medication.
2. Hasten onset of action of antidepressant medication or lithium.
3. Prophylaxis in recurrent mood cycles.
4. Alternative to antidepressant medication.
5. Diagnostic probe.
6. Predictor of response to antidepressant medication or ECT.

# Assessing Competency to Make a Will

James E. Spar, M.D., and Andrew S. Garb, J.D.

*The finding by a court that the author of a will (the testator) lacked mental capacity or was subject to undue influence at the time the will was executed can invalidate the will. A psychiatrist may be asked to assess the competency of a testator when he or she is planning to create or modify a will or after the death of a testator when the will is challenged. To provide guidelines for such evaluations, the authors reviewed the relevant psychiatric, forensic, and legal literature and drew on their own professional experience as well. They outline a systematic approach to the contemporaneous and retrospective evaluation of the elements that affect decisions about mental capacity and undue influence and offer suggestions for the organization and presentation of expert testimony. Awareness of the relevant legal principles and a systematic clinical approach to the assessment can maximize the quality of the psychiatric consultation and expert testimony.*

(Am J Psychiatry 1992; 149:169–174)

The next few decades are likely to bring an increasing call for psychiatric consultation and expert testimony in cases in which the validity of a will has been, or is expected to be, contested on grounds related to the alleged mental incapacity or susceptibility to undue influence of the will's author (the testator). The factor expected to contribute most to this increase is the growing number of Americans who are living through the age of risk for dementing illnesses, such as Alzheimer's disease, that can produce mental changes likely to raise the legal issues we describe in this article. Other factors include increasing public and professional awareness of these conditions and their mental consequences, increasing receptivity by the courts to evidence regarding mental state, and more permissive rules of evidence pertaining to expert testimony on these issues (1).

Despite a growing literature on mental competency and advances in our understanding of and ability to quantify the cognitive and behavioral consequences of late-life mental illness, there are no published guidelines for conducting a psychiatric consultation or giving expert testimony in cases in which mental incompetence or susceptibility to undue influence is, or could be, the basis for contesting a will. This article reviews the relevant legal issues from a contemporary psychiatric perspective and proposes general guidelines for expert consultation and testimony, illustrated by case material drawn from our experience. The aim of these guidelines is to maximize the quality of testimony, regardless of its position on the issues.

## LEGAL CONCEPTS

While there are several legal grounds upon which the validity of a will or codicil (amendment to an existing will) may be challenged, those with the clearest a priori relation to mental illness are the claim that 1) the testator lacked *testamentary capacity* at the time the disputed will or codicil was signed and 2) that specific contents of the will or codicil resulted from *undue influence* exerted upon the testator by one or more persons. Often both allegations are made simultaneously. If lack of testamentary capacity is proven, the entire will or codicil is invalid; if undue influence is proven, those portions of the will or codicil that either result from or cannot be separated from the results of influence are invalid (2).

### *Testamentary Capacity*

The legal concept of testamentary capacity is generally defined throughout the United States as the testator's having sufficient mental capacity to "understand the nature of the testamentary act, understand and recollect the nature and situation of his or her property, and remember and understand his or her relations to his or her living descendants, spouse, and parents, and those whose interests are affected by the will." Many states further require that "the testator is also free of . . . delusions or hallucinations [which] result in the person's devising his or her

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property in a way which, except for the existence of the delusions or hallucinations, he or she would not have done" (3). Minor variations are found in some states; for example, Massachusetts adds the qualifier "in a general way" to the criterion regarding "the nature and situation of his property" (4). However, a few states require only one of the three criteria; for example, Missouri requires only that the testator have "recognized his obligation to the objects of his bounty and their relation to him" (5), and Minnesota requires only that the testator understand "the nature, situation, and extent of his property" and be "able to hold these things in his mind long enough to form a rational judgement concerning them" (6).

### *Undue Influence*

Undue influence is a more complex and less precisely defined concept. To be considered undue, influence must contain an element of "coercion, compulsion or restraint." Mere appeals or arguments, or influence resulting from gratitude or affection, even if the acts creating these feelings were performed selfishly and were designed to affect the testamentary act, do not constitute undue influence. Rather, the testator's mind must be subjugated to that of another, the testator's free agency destroyed, or the testator's volition overpowered by another. While notions such as "subjugated mind" and "overpowered volition" may resist translation into operational criteria for the psychiatric consultant, some states "presume" the existence of undue influence if certain facts are proved, and they require the accused party (the "influencer") to produce evidence to rebut the charges. These facts are 1) the accused party played an active role in procuring the will, 2) the accused party was in a confidential relationship with the testator (e.g., was a close relative or advisor), and 3) the accused party profited unduly under the provisions of the will. In these states undue influence may be presumed even in the absence of mental illness or infirmity, and psychiatric expert testimony may not be necessary. If any of these three factors do not exist, the burden of proof shifts back to the contestant.

Courts have also identified several "indicia" of undue influence, the existence of which will help establish the contestant's case. Most of these indicia have clear implications for the conduct of the psychiatric consultant. They are 1) unnatural provisions in the will, 2) provisions inconsistent with prior or subsequent expressions of the testator's intentions, 3) a relationship between the testator and the beneficiary that created an opportunity to control the testamentary act, 4) a mental or physical condition of the testator that facilitates the subversion of the testator's free will, 5) the beneficiary's active participation in procuring the will, 6) an undue profit to the beneficiary under the provisions of the will, and 7) a confidential relationship between the testator and the beneficiary. These indicia are applicable in most states, even those that do not recognize presumptive evidence of undue influence.

### *The Role of Mental Illness*

The precise relation between mental illness and testamentary capacity and undue influence is nowhere clearly set forth. Case law seems to hold that mental illness may, but does not necessarily, directly impair testamentary capacity. While the testator must have a "sound mind, or sound mind or memory, or sound and disposing mind and memory" (7), still, "old age or forgetfulness, eccentricities or mental feebleness or confusion at various times of the party making the will are not enough in themselves to warrant holding that the testator lacked testamentary capacity" (8).

Despite these judgments, however, Redmond (1) has made the salient observation that "after a person's death questions are easily raised about his or her competence at a particular point in the past if certain medical conditions have been existing. Medical records and other material such as interviews with family almost always provide some basis for an expert opinion that questions the testamentary capacity of the testator. At the same time there is usually insufficient information and documentation on which the expert witness can formulate an opinion that affirms the testator's testamentary capacity at the time of the will making."

The relation between mental illness and undue influence is, as these indicia imply, somewhat less direct: "It requires much less influence to control the will of a person whose functional abilities have been severely impaired by mental illness or by physical conditions which affect mental functioning . . . . A demonstration of impaired mental powers or a clouding of intelligence of the testator makes it easier to establish a charge of undue influence" (9). Besides mental illness per se, aspects of character and personality that do not imply pathology are also important; for example, it is generally more difficult to establish the existence of undue influence if the testator is intelligent and has a strong and independent character than if the testator is dull and has a more passive, malleable character.

While these remarks apply specifically to wills and codicils, basically the same considerations apply to trusts, which continue to grow in popularity as a means for determining the ultimate distribution of one's assets.

## THE PSYCHIATRIST'S ROLE

Psychiatric consultation may be requested contemporaneously with the signing of a will or codicil or later, at the time the will is challenged. In the first situation, the psychiatrist is usually asked by an attorney retained by the testator, a relative, or the spouse to evaluate the testator before he or she signs a will or codicil and to determine whether the testator has testamentary capacity and is free of undue influence. Either someone has raised the possibility of mental illness or there are circumstances (e.g., the testator intends to leave substantial assets to an unexpected party) that prefigure a subsequent challenge of the will. In the second situation, after a will has been contested, the psychiatrist is usually asked to provide advice about how to attack opposing expert testimony and to examine indirect evidence and render a post hoc opinion regarding testamentary capacity and the operation of undue influence.

## CONTEMPORANEOUS EVALUATION

### *The Testator*

The cornerstone of the contemporaneous evaluation of the testator is the clinical interview. Given that the relevant issue is the testator's mental capacity and freedom from undue influence at the precise moment the testamentary document is executed, this interview should be conducted as close as possible to this moment. The longer the elapsed time between the interview and the moment of execution, the greater the risk of an intervening change in mental status and the less weight may be assigned to the expert's testimony by the trier of fact (i.e., the judge or jury). In order to perform the assessment of capacity, the examiner must first determine from informed, objective sources the nature of the testator's assets and, if possible, the names and relationships to the testator of all potential heirs. If necessary, the latter information can be obtained following the interview. Since consultation is usually requested when those making the request expect a finding that the testator has testamentary capacity and is not under undue influence, the presence of one or two disinterested witnesses during the interview may obviate future allegations that the testator's performance was "coached" or otherwise nonrepresentative. If witnesses are present, the interviewer must ensure that they do not distract or influence the testator, and if there is doubt, the interview should be conducted in private. Because this decision could have an impact on the weight of the interviewer's subsequent testimony, as could other "tactical" decisions such as the use of recording devices (discussed later), such decisions should always be made in consultation with the testator's attorney.

Because true mental capacity is demonstrated only by the testator's best possible performance, every effort should be made to establish rapport, reduce anxiety, and maximize the testator's comfort and cooperation. Although the presence of close family members or friends may help achieve these goals, their possible influence on the testator's performance, or even the appearance of such influence, will generally outweigh the benefits afforded by their presence, particularly in cases where undue influence may be an issue.

The examiner should explain the purpose and nature of the interview and indicate what will be expected of the testator. During the interview the interviewer should attempt to assess the specific legal elements of testamentary capacity, identify any features of the testator's personality and mental status that could affect susceptibility to undue influence, and determine the nature, extent, and general functional consequences of mental illness, if any.

A semistructured interview format is recommended, including a comprehensive mental status examination assessing general appearance, dress, and grooming; orientation; recent and remote memory; attention and concentration; receptive and expressive language and speech function; mood, affect, and psychomotor behavior; thought form, flow, and content; insight and judgment; and higher cognitive functions such as calculations and abstractions. Adjunctive administration of standardized instruments such as the Mini-Mental State examination (10), the Neurobehavioral Cognitive Status Examination (11), and the Hamilton Rating Scale for Depression (12), as appropriate, is also recommended. The interview may be audiotaped or videotaped. If it is, the interviewer should attempt to ensure that recording is not intrusive and does not increase the testator's anxiety and adversely affect his or her performance.

To supplement the clinical interview, information should also be obtained from ancillary sources. With the testator's consent, the spouse, other family members, friends, business associates, personal physicians, and the drafter of the will may be interviewed to gain further information regarding the testator's cognitive functioning and reality testing (which bear on the issue of testamentary capacity) and the testator's personality traits, attitudes, goals, and values (which bear on the issue of undue influence). Since the examiner may not be asked to testify about the evaluation for several years, it is important to record sufficient detail of the assessment to facilitate the examiner's future recollection of events.

### *Testamentary Capacity*

The elements of testamentary capacity may be assessed directly by asking the testator to describe his or her assets in as much detail as possible; to articulate his or her understanding of what a will or codicil is and what it does; and to explain who the people named in it are and how they are related to him or her. Because there is no precise legal definition of the terms "recollect" and "remember," the consultant should assess unassisted recall, prompted recall, and recognition memory. The testator who cannot recall one or more of the elements we have mentioned should be prompted (i.e., given "hints"), the specific content of which should be recorded (e.g., "What about stock in large corporations?"). If the testator cannot recall an element even with hints, he or she should be given the opportunity to demonstrate recognition knowledge by selecting responses from a list that contains the correct items and several feasible but incorrect distracters; for example, "A will is 1) a statement about how you feel about your relatives, 2) instructions for how your property should be distributed after your death, 3) a promise to pay you a certain amount of money if you get hurt, 4) a paper that tells you your bank balance" or "Which things on this list do you own? 1) a house in Westwood, 2) a house in Malibu, 3) an apartment building in Santa Monica." The stimulus lists should be saved for future reference, and responses should be recorded verbatim.

Although recognition knowledge alone is not likely to be accepted as evidence of retained mental capacity, lack of such ability may help to establish lack of capacity. Accordingly, the distracters should not be so obviously incorrect as to "guide" the testator to the correct answer, and the probability of a correct guess must be taken into account. To minimize the possible effects of "coaching" and sporadic situational factors that may detract from the testator's initial performance, this part of the evaluation should be administered twice, with the administrations separated by at least 5 minutes of unstructured interview.

The interviewer should also focus on contents of the testamentary document that are identified by counsel as likely to be challenged. This is done by asking the testator to discuss the reasons and motives behind each such decision. These responses will form the basis for the examiner's assessment of the testator's grasp of circumstances, use of logic and reason, and capacity for reality testing.

### *Undue Influence*

Thorough assessment of the possible exertion of undue influence requires examination of the testator as we have described, along with assessment of the testator's physical and social circumstances. This assessment should focus on the indicia of undue influence that we have listed, as well any other features that may be conducive to control and manipulation of the testator's emotions, beliefs, and behavior. The literature on contemporary religious cults may be helpful in this regard. For example, Streiker (13) listed elements commonly used by such cults that he describes as "a formula for evoking instant conversion" to the belief system of a group. Although some of these elements may occur in any intimate relationship, their coercive power appears to increase when they are applied simultaneously and persistently. They include secluding; providing attention, affection, and approval; encouraging behavioral regression and dependency; depriving mental and physical privacy; repeatedly presenting an organized body of data (indoctrination); reinforcing new behaviors consistent with desired beliefs; and discouraging independent thought by negative characterization.

The clinical examination should focus on any content areas related to the testamentary document that evoke hesitancy, uncertainty, or inconsistency on the part of the testator (e.g., "You seem uncertain about the decision to leave so much of your estate to Smith. How did you arrive at that decision?" or "You've indicated that you have not been a religious person, yet you are intending to leave a substantial amount of money to a religious organization. Can you explain this?"). Similarly, one should explore in detail the testator's thoughts and feelings about natural heirs who are to be disinherited or treated less favorably than may be expected or individuals who are unexpectedly named as beneficiaries.

*Case 1.* Mildred had always been Ms. A's favorite daughter, while Ms. A had always been critical of and did not get along with her other daughter, Edith. When Ms. A was 82 years old and had become legally blind, crippled, and completely dependent on others for existence, Edith volunteered to move into her mother's very expensive house to be her caretaker. Although Ms. A resented this arrangement and continued to be critical of Edith's habits, after about a year Edith arranged for Ms. A to change her long-extant will and bequeath the house to her rather than to Mildred. Mildred asked Ms. A's attorney to arrange for psychiatric evaluation of her mother. When the topic of which daughter was to get the house came up during the evaluation, Ms. A became anxious and uncomfortable, made several inconsistent statements, and appeared to exaggerate what had been, up to that point, only mild memory and language difficulties, as if to evade the question by being "unable" to understand it. In light of the physical and social circumstances, the psychiatric consultant gave the opinion that Ms. A was under Edith's undue influence.

## RETROSPECTIVE EVALUATION

### *Testamentary Capacity*

Because direct evidence is often not available, retrospective evaluation of testamentary capacity may be entirely inferential. However, despite the pessimistic note registered by Redmond (1) that we have cited, in many cases descriptive information provided by the surviving spouse, friends, relatives, business associates, and service providers regarding the testator's behavior can be very informative. Similarly, medical records, business records, and personal documents such as family films and videotapes, along with checkbook records, personal correspondence, notebooks and diaries, and even the will itself (if it is "holographic," i.e., handwritten), which directly reflect the testator's mental capacity, may provide data adequate to support a reasonably strong inference regarding testamentary capacity.

Medical records may contain formal diagnoses of mental or physical illnesses that could compromise mental function. If they do, it is important to scrutinize the records for descriptions of the testator's behavior and documentation of formal clinical examination of mental status, psychological tests, or other data that support the diagnoses and indicate lost and preserved mental capacities and the presence or absence of delusional beliefs. It is often fruitful to interview also the authors of the record, who may clarify or supplement the information presented.

*Case 2.* Ms. B was discharged from a psychiatric ward weeks before she amended her will and left all of her property to the manager of the board-and-care home where she was to spend the last months of her life. Her niece, the only surviving heir, challenged the will on the basis of lack of testamentary capacity and insane delusion. The medical record contained nursing notes indicating that Ms. B, in 6 weeks of hospitalization, was never able to find her own room on the ward, could not distinguish her own clothes from those of her roommates, never learned her nurse's name, and consistently thought she was in a different state. Physicians' notes indicated that Ms. B thought that her niece was "in cahoots with the Mafia and was trying to have her killed." She had also expressed the belief that her niece was actually dead and had been replaced by an impostor. On the basis of this record, supported by deposition testimony, the consulting expert gave the opinion that Ms. B lacked testamentary capacity and that the codicil was the product of an insane delusion.

Other records, including notes of the attorney who prepared the will or codicil, based on his or her meetings and conversations with the testator, may also provide valuable evidence relating to testamentary capacity. In most states this material is held to be accessible (i.e., no longer privileged) after the testator's death if the issue of capacity is raised. Records that contain entries made by the testator or that reflect the testator's unassisted knowledge and judgment may provide direct evidence of the testator's memory, language and higher intellectual functioning, judgment, and visuospatial skills.

*Case 3.* Ms. C's heirs challenged the validity of her will on the basis of lack of testamentary capacity, which they claimed was demonstrated by her sale of a valuable piece of income property a few months before her death. During this period she suffered some impairment in memory and self-care, which the expert was able to characterize as quite mild. However, because the sale price of the income property was significantly below market value, the contestants maintained that Ms. C, known for her shrewdness and business sense, could not have agreed to such a price unless she was intellectually impaired enough to lack testamentary capacity also. After examining several of Ms. C's personal notes and documents related to the sale, the consulting expert was able to determine, with the assistance of a tax expert, that the details of the transaction (including the price) were carefully calculated to effect a quick sale that would take advantage of an anticipated change in the tax law. Had Ms. C lived, the actual sale would have been more to her financial advantage than a sale for a higher price that might have taken a few more months to complete. The transaction, in light of the expert's other observations, provided strong evidence that Ms. C's judgment and reasoning ability were relatively intact, in spite of her failing memory and capacity for self-care.

Deposition testimony of the surviving spouse, friends, relatives, business associates, and involved professionals regarding the testator's behavior may supplement information obtained by direct interview, particularly if the psychiatric consultant has the opportunity to advise counsel regarding the most fruitful content areas to explore when taking the depositions. Again, the most valuable information from such sources is information related to the testator's behavior at or near the moment that the challenged testamentary document was signed.

Interpretation of data from these sources necessarily depends mainly on the expert's clinical experience with similarly affected individuals, as there is very little scientific or clinical literature that correlates cognitive capacities relevant to one area of functioning with those of another. However, a few studies correlating behavioral and cognitive capacities in patients at different stages of Alzheimer's disease (14) may be of value in some cases in which Alzheimer's disease is the probable diagnosis.

### *Undue Influence*

The relevant issue in retrospective determination of undue influence is, Did the testator suffer mental illness that rendered him or her particularly susceptible to undue influence at or before the time the challenged testamentary document was signed, and were personality features and social and environmental factors during the same time period more or less conducive to the exertion of undue influence? Again, in the absence of published research indicating which mental illnesses affect susceptibility to influence, the expert must rely on clinical experience. The experience of one of us (J.E.S.) suggests that any debilitating mental or physical illness resulting in dependence on caretakers will increase susceptibility to influence, while conditions associated with impaired critical judgment (such as mania or hypomania) or impaired reality testing (such as delusional disorder or schizophrenia) seem to reduce patients' ability to resist influence even in the absence of significant dependency. Dementias of all types, depending on the stage, seem to increase susceptibility to influence through effects on judgment and reality testing, whereas they reduce susceptibility to the extent that suspiciousness, paranoia, and exaggerated premorbid character traits (such as stubbornness, suspiciousness, and irascibility) are present. The effects of other psychiatric conditions and of other individual personality traits and constellations thereof on susceptibility to influence appear to be more variable. The psychiatric consultant should be prepared to formulate an opinion that takes into account the indicia of undue influence, the testator's personality traits, signs and symptoms of mental illness, and their effect on susceptibility to influence.

*Case 4.* Ms. D's grandchildren sued to overturn her will, in which she left her entire estate to her husband of only 5 years. The basis of the claim was that her husband, 50 years her junior, had exerted undue influence so as to cause her to be angry with and ultimately disinherit the grandchildren. Deposition testimony of Ms. D's friends and neighbors indicated that she had been independent to the point of belligerence and had consistently expressed her love and admiration for her husband, over whom she was seen as quite domineering. The consulting psychiatrist was also given access to more than 100 cards and letters exchanged by Ms. D and her daughter (deceased at the time of trial) and grandchildren over a 7-year period. These documents clearly revealed longstanding and increasing enmity between Ms. D and her daughter and grandchildren that preexisted the entry of Ms. D's husband into her life. This enmity did not increase after he entered the picture; rather, his influence, as reflected in the cards and letters, appeared to soften Ms. D's hostility toward her natural heirs. The consultant's opinion was that conditions favoring influence did not exist and that Ms. D left her money to her husband so that her natural heirs would not get it.

## ORGANIZING TESTIMONY

Expert testimony must initially establish to the court's satisfaction that true expertise exists in the area of the proffered testimony, that the witness has a legitimate claim to such expertise, and that such expertise is needed in order to arrive at the witness's conclusions. When allowed to testify, experts can present opinions as evidence, even if the opinions are based on information that would not otherwise be admissible (e.g., hearsay), as long as the information and the methods used to gather it are of the type reasonably relied upon by experts in the same field. As a general principle, expert testimony is strengthened if the expert presents the factual basis for his or her opinions, avoids technical jargon whenever possible, and acknowledges the limits of his or her expertise.

With these considerations in mind, we propose the following rules of thumb, which aim at enhancing the clarity and quality of expert testimony but are not intended to replace appropriate consultation between the expert and the attorney. An opinion about testamentary capacity, whether based on examination of the living testator or on retrospective review of evidence, should include comment on 1) the testator's global mental status, supported where possible by scores on standardized instruments; 2) the specific aspects of the testator's mental functioning believed to be most germane to the question of testamentary capacity (e.g., orientation, recent and remote memory, expressive and receptive language functioning, reality testing, judgment and reasoning); 3) the implications of these observations with respect to the specific elements of testamentary capacity (i.e., understanding the nature of the testamentary act, remembering and understanding relatives and assets); and 4) a diagnostic impression.

If the testator meets the criteria for a psychiatric diagnosis but retains testamentary capacity, the expert is advised to clarify the distinction between that diagnosis per se and the testator's level of functioning. This testimony is recommended to offset the commonly held false assumption that certain conditions (e.g., Alzheimer's disease) automatically render their victims incompetent for any decisions. Noting how this misassumption regarding Alzheimer's disease has permeated the fabric of law and judicial procedure, Rosoff and Gottlieb (15, p. 12) stated, "Laws and procedures currently followed in many states are inflexible and insensitive . . . and do not distinguish appropriately among the various levels of a person's competence." In this regard the expert may wish to cite examples—such as the college professor or corporate executive with Alzheimer's disease who is still able to function, albeit with reduced effectiveness in his or her professional role—in order to facilitate the judge's or jury's understanding that an individual with this illness may retain testamentary capacity despite the diagnosis.

Testimony regarding undue influence is structured similarly, covering 1) the testator's personality and global mental status; 2) specific personality traits, functional symptoms, cognitive deficits, and physical and social circumstances that could affect susceptibility to influence; 3) the implications of these in light of the elements of presumptive undue influence, the "indicia" of undue influence, and any perceived discrepancies between testamentary content and the testator's attitudes, goals, and values; and 4) a diagnostic impression.

To "wrap up" the direct examination, counsel may elicit the expert's opinion on the "ultimate issues" of the case, namely, whether the testator possessed testamentary capacity and whether he or she was free from undue influence. Although it was formerly within judicial authority to prohibit such testimony (on the theory that to give such opinions is, in effect, to render a legal judgment and thereby usurp the role of the trier of fact), the trend in recent years has been to follow rule 704(a) of the *Federal Rules of Evidence,* which states, in part, "Testimony in the form of an opinion or inference otherwise admissible is not objectionable because it embraces an ultimate issue to be decided by the trier of fact" (16), and the "helpfulness standard" (17), which essentially allows experts to provide any testimony within their range of expertise that will "aid the trier of fact in his search for the truth."

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# Community Mental Health and Mental Retardation Services in the United States: A Comparative Study of Resource Allocation

**David Braddock, Ph.D.**

*Objective: Preliminary studies suggest that during the 1980s, spending for community mental retardation services in the United States may have grown much more rapidly than spending for community mental health. The primary objective of this study was to test empirically the validity of this thesis on a national basis. An additional objective was to determine why such a distinction in community spending patterns might have evolved nationally. Method: The study used states as the units of analysis and employed a five-factor hierarchical regression to predict variance in mental health and mental retardation spending. Factors were state size, state wealth, degree of federal assistance, state civil rights activity, and strength of consumer advocacy groups. Strong roles for the civil rights and consumer advocacy factors were hypothesized. A collateral opinion survey in the 10 states exhibiting the greatest within-state difference in community mental health and mental retardation spending was also completed. Results: Community mental retardation spending grew nearly four times more rapidly than community mental health spending in the 1980s. The consumer advocacy and civil rights factors were strongly associated with spending for community mental retardation services in the states, but these factors did not predict spending for community mental health services. Conclusions: Study recommendations included strengthening mental health family and consumer advocacy groups in the states and promoting systematic exchange between the mental health and mental retardation fields through joint state planning initiatives, studies, and conferences. The need for Medicaid reform is a unifying theme in both the mental health and mental retardation fields.*

(Am J Psychiatry 1992; 149:175–183)

For 221 years the U.S. state governments have been authorized by law to allocate funds for the care of persons with mental disabilities (1). For most of this period, the quantity of state government resources allocated for mental health services has dwarfed the level of funding available for mental retardation services. Thirty years ago, for example, the Illinois Department of Mental Health allocated $61 million for mental health services and $11 million for mental retardation programs (2). In the 1970s, the federal government became actively involved in financing services for persons with mental retardation through the adoption of the reimbursement program of the Medicaid Intermediate Care Facilities for the Mentally Retarded. Extensive class action litigation, coupled with vigorous advocacy

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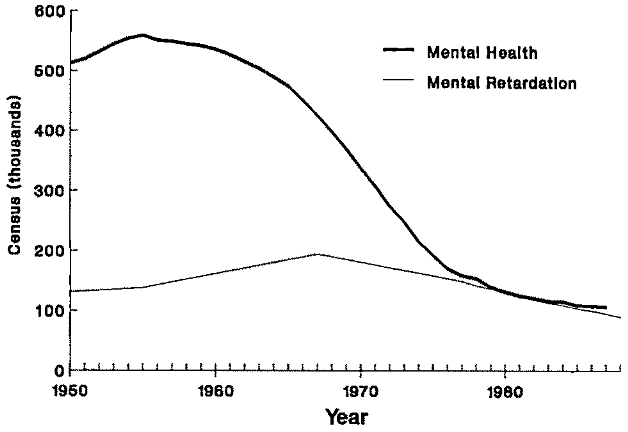
**FIGURE 1. Daily Census of State Mental Institutions: 1950–1988**[a]



[a]Mental health data from Witkin (5); mental retardation data from Lakin (6) for 1950–1976 and from Braddock et al. (3) for 1977–1988.

by associations for retarded citizens, helped stimulate a dramatic expansion of mental retardation resources in the states. By fiscal year 1983, a roughly equivalent sum of money—$6.93 billion versus $6.81 billion—was being budgeted across the country in state agency programs that served persons with mental retardation and closely related developmental disabilities (3) and in state mental health programs (4), respectively.

As shown in figure 1, roughly comparable numbers of individuals were being served nationally in 1988 in terms of the average daily census in state-operated mental retardation and mental health institutions. In contrast, community mental retardation services grew at an unprecedented rate in the states during the 1980s (3, 7–9). In 1977, the resident census in the nation's 4,290 community mental retardation residential facilities was 62,397 (10). In 1988, according to a national study by the University of Illinois at Chicago, more than 174,000 mentally retarded persons resided in community residential settings, excluding nursing homes (3). The total number of community mental retardation residential facilities exceeded 15,000 units in 1982 (11) and 28,000 units in 1988 (8). Recent assessments, however, have consistently stressed the limited development of supported community living for persons with mental illness in the states (12–19). In its widely disseminated "Proposal for Public Policy on the Chronic Mental Patient," APA described the lack of community mental health services as a "national crisis" (14, p. 209).

## APPROACH

The central purpose of this study was, using state governments as the basic unit of analysis, to compare recent trends in public spending for mental health and mental retardation services in the United States. Guiding the study was a strong suspicion that funding for community mental retardation services at the state level was, throughout the 1980s, growing much more rapidly and had achieved much greater total volume than had similar funding for community mental health services. Assuming that this was true, the important research question then was: why does this distinction in spending exist and what can be done to spur the development of community mental health services in the states using lessons learned from the recent expansion of community mental retardation services?

A substantial body of theory in mental health research literature ascribes a critical role to consumer advocacy groups, such as the Association for Retarded Citizens of the United States and the National Alliance for the Mentally Ill (NAMI), in stimulating the growth of community services (15, 17, 18, 20–22). Studies in juvenile delinquency (23), consumer protection (24), unemployment compensation (25), and, more recently, in mental retardation (26) have identified interest group activity as an important covariate of innovative state programs and spending policies in these fields. In mental retardation, associations for retarded citizens have operated professionally staffed government affairs units influencing public appropriations policies since the late 1950s. Associations for retarded citizens, in fact, were often the moving parties or plaintiff interveners in key litigation in the states. Thirty-eight right-to-habilitation class action lawsuits in mental retardation were filed in 27 states and the District of Columbia between 1971 and 1980 (27). Similar cases were litigated throughout the 1980s (e.g., *Homeward Bound, Inc. v. Hissom Memorial Center*) (28). This litigation frequently resulted in court orders or consent agreements virtually compelling defendant state agencies and governors to request substantially increased legislative appropriations for mental retardation services (29).

In a study of seven states, Wilson and Kouzi (20) attributed the "superior conditions of the homes for the developmentally disabled" and their higher mean funding level per client to the "relatively strong political position of national organizations that lobby for the interests of persons with these disabilities" (p. 317). Elpers (30) credited "relatives of the developmentally disabled" and their "powerful lobby" as an important basis for California's favored budgeting of funds for this group in recent years (p. 803). Winkle's New Jersey study (31) found that local organizations advocating for the interests of individuals with developmental disabilities were more likely than local mental health organizations to have family members instead of professionals or concerned citizens on their boards. Local organizations for individuals with developmental disabilities were also more likely to be associated with national and state organizations. Ross (32), a Washington lobbyist with experience in developmental disabilities and mental health organizations, has noted the relatively greater political strength of mental retardation and developmental disabilities advocacy groups nationally. He attributed this greater strength to the more extensive involvement of family members in developmental disabilities advocacy groups. Wilson and Kouzi (20) speculated that the social stigma accompanying mental illness (21, 33, 34) has inhibited community mental health advocacy more than stigma has inhibited the development of advocacy groups in the mental retardation field.

Bachrach (35) has observed that the civil rights advocacy movement has been a more potent instrument of community integration in the mental retardation field than in mental health. The social reform ideology of civil rights, according to Bachrach, is only one of several important factors giving rise to the deinstitutionalization of persons with mental illness. Other crucial factors include the introduction of antipsychotic medications and the development of crisis intervention techniques.

## METHOD

### *Analysis of Spending*

The present study was designed to test empirically Bachrach's assumption about the different roles of civil rights in the mental health and mental retardation fields and also to investigate the impact of consumer advocacy on public spending in both fields. The initial task was to compare the budgetary outputs of state political systems for mental health and mental retardation services. State government executive budget data for fiscal years 1981, 1983, 1985, and 1987 were employed for this purpose. Data sets for mental health and mental retardation spending in the states were obtained from the National Association of State Mental Health Program Directors (4) and the University of Illinois at Chicago (3). Minor modifications in the two data sets, described in a monograph available from me, were implemented to improve data comparability. Next, mental health and mental retardation fiscal effort indices were computed for each of the states for institutional and community services. This involved dividing each state's total spending for mental health and mental retardation services by that state's aggregate annual personal income. Statewide personal income data were obtained from the U.S. Bureau of Economic Analysis. Fiscal effort was computed for fiscal years 1981, 1983, 1985, and 1987 and also cumulatively across the entire 7-year period. Data were expressed in real economic terms (36).

### *Predictors of Community Spending*

Fiscal effort across fiscal years 1981–1987 served as the dependent variable in two hierarchical regressions—one for community mental retardation spending in the states and one for community mental health spending. The predictors included state size, state wealth, and degree of federal financial assistance for community programs. These factors have been commonly associated with state government spending in education, public welfare, corrections, natural resources, and transportation (3). However, the three predictors did not predict state-to-state variance in community mental retardation spending in a preliminary study (37). Gray's civil rights index (38) was significant in predicting community mental retardation fiscal effort in a subsequent study (26), and it was employed in both regressions in the present study. The civil rights index measured the rapidity of adoption of three state civil rights laws in public accommodations, fair housing, and fair employment practices.

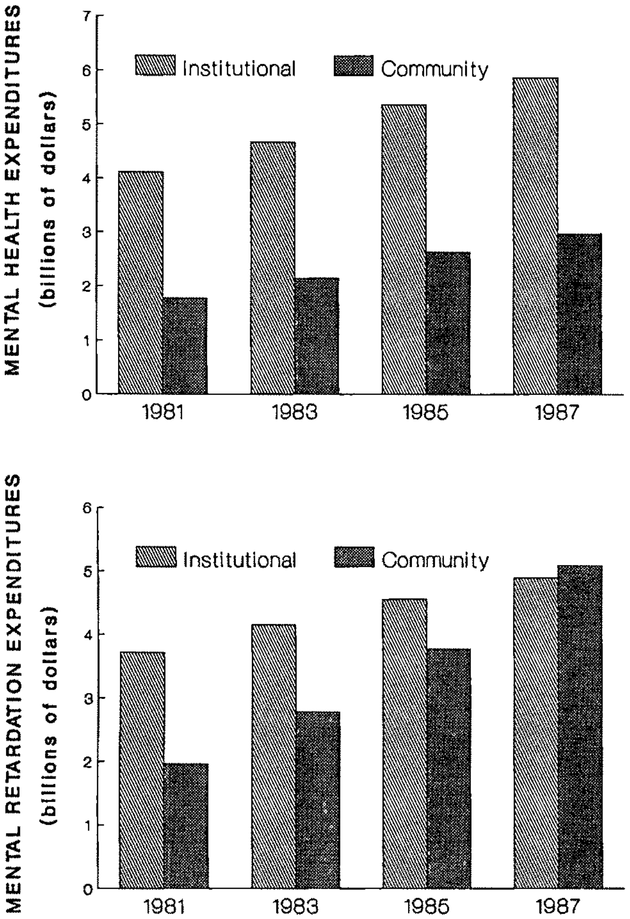
The fifth variable in the regression equation, consumer advocacy, was operationalized in terms of per capita membership in state chapters of the Association for Retarded Citizens of the United States and in NAMI. NAMI is a family-based consumer organization concerned with serious mental illness. Like units of the Association for Retarded Citizens, NAMI membership consists primarily of relatives of persons with challenging mental disabilities. Torrey et al. (18) wrote that NAMI was "the single most important political force to emerge for the seriously mentally ill in this century" (p. 100). Chandler (15), Lefley (21), and Santiago (17) also specifically acknowledged NAMI's growing political significance in influencing state and federal policy in the mental disabilities field during the 1980s. A special telephone survey of membership in state and local NAMI chapters was conducted for the present study, whereas the Association for Retarded Citizens of the United States provided state-by-state membership figures. Consumer advocacy in the Association for Retarded Citizens and NAMI was computed on the basis of 1988 state membership as a percentage of each state's general population (39).

A second, paired set of regression analyses was also conducted on institutional fiscal effort in the states. The purpose of this second set of analyses was to contrast the five-factor regression across both the community and institutional sectors. The same five predictors employed in the two community mental health and mental retardation regressions—state size, wealth, federal assistance, civil rights, and consumer advocacy—were also employed in the institutional regressions.

### *Definitions*

*Institutional spending for mental retardation services* included operating funds from the Intermediate Care Facility for the Mentally Retarded program and state general revenue for state-operated institutions with 16 beds or more, developmental centers, training centers, state schools, and mental retardation units in state psychiatric hospitals (N=290). *Institutional spending for mental health services* included state general revenue and Medicaid and Medicare for treatment and services in 284 state psychiatric hospitals. *Community mental retardation spending* consisted of federal and state funding for publicly or privately operated community residential facilities and for nonresidential services such as habilitation, day training, sheltered work, supported and competitive employment, family support, early in-

**FIGURE 2. Expenditures for Institutional and Community Services in the United States: Fiscal Years 1981, 1983, 1985, and 1987**[a]



[a]Mental health data adapted from the National Association of State Mental Health Program Directors (4, tables 40 and 41); mental retardation data adapted from Braddock et al. (3).

tervention, and case management (3). *Community mental health spending* included federal and state funds for programs administered by state mental health agencies that supported treatment, rehabilitation, and residential care in community settings.

## RESULTS

### *Analysis of Trends*

During the 1980s, community mental retardation services were funded with greater intensity in the states than were community mental health services. Between fiscal years 1981 and 1987, state government spending for community mental health services increased 27% in real economic terms. In the same period, real spending for community mental retardation services increased by 96%. Unadjusted spending for community mental retardation state government general fund commitments from own-source state revenues (i.e., excluding federal funds) increased by $2.2 billion during fiscal years 1981–1987; state general fund own-source support for community mental health services grew by $0.93 billion over the same period. Growth in state mental retardation spending was further enhanced by an acceleration in funding for community services through the federal Intermediate Care Facilities for the Mentally Retarded and Home and Community-Based Services Waiver programs. Federal Intermediate Care Facilities for the Mentally Retarded reimbursements, excluding state matching funds, advanced from $244 million to $842 million between fiscal years 1981 and 1987. Initiated in fiscal year 1982, federal Home and Community-Based Services Waiver funds for mental retardation grew from $1.2 million to $166 million in fiscal year 1987 (3). By fiscal year 1991, the mental retardation Home and Community-Based Services Waiver program served 48,000 clients in 43 states and involved nearly $900 million in state and federal expenditures (40). Home and Community-Based Services Waiver funding for mental health services was $792,000 in fiscal year 1987 (41, 42).

Trends in spending for both institutional and community services in the United States during fiscal years 1981–1987 are illustrated in figure 2. In fiscal year 1987, total spending for mental retardation services in the states was $9.98 billion versus $8.83 billion for mental health. Community mental retardation outlays in fiscal year 1987 were 72% higher than those for community mental health ($5.08 billion versus 2.96 billion). Wide variations among the states in spending for community services as a share of statewide personal income were observed. In fiscal year 1987, community mental health spending levels ranged from $1.98 to $0.06 per $1,000 of personal income in Massachusetts and Iowa, respectively; community mental retardation spending levels ranged from $3.31 to $0.41 in North Dakota and Nevada (table 1). Mean expenditures in the United States for community mental health and mental retardation services were $0.82 and $1.40 per $1,000 of personal income, respectively.

It was initially suspected that the ratio of mental retardation funds allocated for community and institutional services in the nation would be larger than the ratio of funding for mental health services. This was confirmed. The proportional relationship nationally between cumulative (fiscal years 1981–1987) mental retardation and mental health funding for community and institutional services was 44% versus 56% (mental retardation) and 32% versus 68% (mental health). These percentages for community and institutional spending, respectively, reflect the adjusted *cumulative* trend for the 7-year period. They do not, however, reflect the *direction* of the trend. Between fiscal year 1981 and fiscal year 1987, community mental retardation spending as a percentage of total mental retardation spending increased from 35% to 51%. In contrast, during the same period, spending for community mental health services as a percentage of total mental health spending grew from 30% to 34%. Moreover, much of the percentage growth in mental health spending was

**TABLE 1. Expenditures for Community Mental Health and Mental Retardation Services in the United States: Fiscal Year 1987[a]**

| Mental Health | | | Mental Retardation | | |
|---|---|---|---|---|---|
| Rank | State | Expenditure per $1,000 Annual Personal Income (dollars) | Rank | State | Expenditure per $1,000 Annual Personal Income (dollars) |
| 1 | Massachusetts | 1.98 | 1 | North Dakota | 3.31 |
| 2 | Vermont | 1.76 | 2 | Rhode Island | 3.14 |
| 3 | Wisconsin | 1.56 | 3 | District of Columbia | 2.97 |
| 4 | District of Columbia | 1.55 | 4 | New York | 2.91 |
| 5 | New Hampshire | 1.36 | 5 | Minnesota | 2.87 |
| 6 | Michigan | 1.29 | 6 | Connecticut | 2.46 |
| 7 | North Carolina | 1.26 | 7 | New Hampshire | 2.12 |
| 8 | North Dakota | 1.24 | 8 | Michigan | 2.09 |
| 9 | Washington | 1.19 | 9 | Pennsylvania | 2.07 |
| 10 | Missouri | 1.14 | 10 | Maine | 2.02 |
| 11 | West Virginia | 1.14 | 11 | Vermont | 1.90 |
| 12 | Rhode Island | 1.10 | 12 | South Dakota | 1.87 |
| 13 | Minnesota | 1.07 | 13 | Montana | 1.84 |
| 14 | California | 1.05 | 14 | Massachusetts | 1.83 |
| 15 | Alaska | 1.02 | 15 | Ohio | 1.79 |
| 16 | Indiana | 0.92 | 16 | Nebraska | 1.77 |
| 17 | Hawaii | 0.90 | 17 | Louisiana | 1.64 |
| 18 | Utah | 0.88 | 18 | Iowa | 1.60 |
| 19 | Maine | 0.87 | 19 | Wisconsin | 1.47 |
| 20 | Oklahoma | 0.85 | 20 | Colorado | 1.46 |
| 21 | South Carolina | 0.85 | 21 | Wyoming | 1.41 |
| 22 | Pennsylvania | 0.84 | 22 | Idaho | 1.24 |
| 23 | New York | 0.81 | 23 | Utah | 1.21 |
| 24 | Ohio | 0.81 | 24 | Maryland | 1.20 |
| 25 | Kentucky | 0.77 | 25 | New Jersey | 1.19 |
| 26 | New Mexico | 0.74 | 26 | Illinois | 1.19 |
| 27 | Arkansas | 0.72 | 27 | Alaska | 1.16 |
| 28 | Oregon | 0.72 | 28 | Indiana | 1.11 |
| 29 | Florida | 0.68 | 29 | Missouri | 1.06 |
| 30 | Connecticut | 0.63 | 30 | Oregon | 1.05 |
| 31 | Nevada | 0.62 | 31 | Georgia | 1.02 |
| 32 | South Dakota | 0.61 | 32 | South Carolina | 1.01 |
| 33 | Colorado | 0.61 | 33 | Florida | 0.98 |
| 34 | Louisiana | 0.58 | 34 | California | 0.97 |
| 35 | Arizona | 0.56 | 35 | Washington | 0.92 |
| 36 | Wyoming | 0.56 | 36 | Kansas | 0.88 |
| 37 | Alabama | 0.56 | 37 | North Carolina | 0.87 |
| 38 | Tennessee | 0.53 | 38 | Kentucky | 0.87 |
| 39 | Montana | 0.53 | 39 | Arkansas | 0.85 |
| 40 | Idaho | 0.52 | 40 | New Mexico | 0.84 |
| 41 | Illinois | 0.52 | 41 | Arizona | 0.81 |
| 42 | Georgia | 0.51 | 42 | West Virginia | 0.79 |
| 43 | New Jersey | 0.50 | 43 | Delaware | 0.77 |
| 44 | Maryland | 0.46 | 44 | Oklahoma | 0.75 |
| 45 | Delaware | 0.44 | 45 | Mississippi | 0.74 |
| 46 | Virginia | 0.44 | 46 | Texas | 0.72 |
| 47 | Mississippi | 0.38 | 47 | Hawaii | 0.55 |
| 48 | Texas | 0.30 | 48 | Tennessee | 0.53 |
| 49 | Nebraska | 0.29 | 49 | Alabama | 0.53 |
| 50 | Kansas | 0.28 | 50 | Virginia | 0.51 |
| 51 | Iowa | 0.06 | 51 | Nevada | 0.41 |
| | United States | 0.82 | | United States | 1.40 |

[a] Mental health data adapted from the National Association of State Mental Health Program Directors(4); mental retardation data adapted from Braddock et al. (3).

attributed to the deployment of Alcohol, Drug Abuse, and Mental Health Administration Block Grant funds directly to state mental health agencies after fiscal year 1982. Before August 1981 these funds were allocated directly by the federal government to community mental health agencies. In fiscal terms, state mental retardation agencies were involved in a more dynamic transformation from institutional to community services than were their counterparts in mental health.

### *Results of Regression Analyses*

Results of the community mental health regression were not statistically significant. State size, state wealth, federal aid, civil rights activity, and consumer advocacy failed to account for any appreciable variance in the equation (F=1.16, df=5, 39, p>0.05. A modest simple correlation (r=0.30, p<0.05) was observed between community mental health spending and the civil rights factor. The regression of state size, state wealth, federal aid, civil rights innovativeness, and Association for Retarded Citizens consumer advocacy was statistically significant for community mental retardation spending ($F=8.42$, $df=5, 42$, $p<0.001$). Fifty percent of the variance in the regression equation was accounted for. However, the advocacy and civil rights factors accounted for over 90% of this explained variance. State size, state wealth, and federal aid for community programs were not significant predictors in the mental retardation regression ($F=0.74$, $df=2, 42$, $p<0.05$).

Hierarchical regression analyses were also carried out for institutional fiscal effort in mental health and mental retardation. Neither yielded a statistically significant overall equation ($F=1.84$, $df=5, 42$, $p>0.05$ and $F=2.09$, $df=5, 42$, $p>0.05$, respectively). The Association for Retarded Citizens consumer advocacy factor did account for a statistically significant increment in predicted variance in the institutional regression equation ($F=9.59$, $df=1, 42$, $p<0.01$). Thus, a higher per capita rate of state Association for Retarded Citizens membership was associated with a greater level of fiscal effort for both community and institutional mental retardation services in the states.

### *Collateral Survey of 10 States*

Collateral evidence of the degree to which various factors might account for state-by-state variance in fiscal effort for community mental health and mental retardation services was explored in a telephone survey involving 40 individuals from those 10 states exhibiting the greatest within-state percentage variance in community mental health and mental retardation spending in fiscal year 1987. All 10 states expended more funds for community mental retardation services than for community mental health. The interviewees included four representatives from each of the 10 states: two executives from the community services component of the state mental health/mental retardation agencies, including one program leader from the mental retardation division and one from the mental illness division; and two from the consumer advocacy sector, including one from the state Association for Retarded Citizens chapter and one from the state NAMI office. The 10 states were Colorado, Connecticut, Iowa, Maine, Maryland, Michigan, Montana, Nebraska, New York, and Pennsylvania.

The survey probed reasons underlying these states' relatively greater funding levels for community mental retardation services. The interviewer randomly listed several potential reasons including favorable federal government policies; strength of consumer advocacy groups; effect of class action litigation; and leadership of key legislators, state agency directors, governors, and the media. In addition, interviewees were asked to identify other factors creating the wide disparity in the proportion of funding allocated in their state for community services. All 40 interviewees' comments were transcribed by the interviewer and categorized. A second analyst independently attempted to replicate the classification of the first in a reliability assessment using the kappa statistic (kappa=0.97) (43).

Thirty-five of the 40 respondents (88%) stated that Association for Retarded Citizens advocacy was an important factor in the greater level of financial commitment in their state for community mental retardation services. Extent of agreement between the mental health and mental retardation respondents on the importance of the Association for Retarded Citizens advocacy factor was high (kappa=0.72). All four respondents from each of eight states and three of four from a ninth state cited the crucial importance of the Association for Retarded Citizens consumer advocacy factor. The impact of class action litigation in mental retardation and the increased stigma of mental illness were also cited frequently by the respondents (18 and 15 times, respectively).

## CONCLUSIONS AND IMPLICATIONS

### *Divergent Patterns of Community Spending*

Widely divergent community mental health and mental retardation spending patterns in the states were identified in this study. Analysis of the predictors of spending underscored these differences. Political culture in the states, as represented by the civil rights index in the regression analyses, was a major covariate of mental retardation spending, yet it was only weakly correlated with mental health fiscal effort. This finding is consistent with Bachrach's observation (35) about the more potent influence of civil rights in the mental retardation field. Remarkably, the 10 most highly ranked states in community mental retardation fiscal effort for fiscal year 1987 (table 1) were each the site of major class action right-to-habilitation litigation. In four of these 10 states (North Dakota, New York, Connecticut, and Michigan) the state Association for Retarded Citizens chapter was the moving party in the case. Associations for retarded citizens were plaintiff interveners in Rhode Island, New Hampshire, and Pennsylvania; *amicus curiae* in Minnesota; and the court monitor in the Washington, D.C., case.

Consumer advocacy was an important predictor of community mental retardation spending; however, it was not significant in the mental health regression. Why the predictive power of the consumer advocacy factor should be so different across the mental health and mental retardation sectors is a provocative question. There are several plausible hypotheses. NAMI formed nationally in June 1980 (44). During the period of this analysis, most NAMI chapters lacked the membership base, operating experience, and professional government affairs components enjoyed by state and national Association for Retarded Citizens units. The failure of the consumer advocacy factor to predict any variance in the community mental health regression might well be attributed to the brief tenure of NAMI as a functioning organization and to the emphasis in this analysis on identifying nationwide variance in the regression. Had the study focused in greater depth on NAMI's activities in specific states, discovering relationships between NAMI's activities and enhanced community spending in those states would have been more likely (17). In Maryland, for example, NAMI's activities as part of a citizens' advocacy coalition were instrumental in securing an increase in the state's community mental health budget from $20.4 million in fiscal year 1983 to $55.2 million in fiscal year 1988 (45).

Mental health organizations such as NAMI and the National Mental Health Association may lack the singularity of focus of the associations for retarded citizens on a community integration agenda (45, 46). The Association for Retarded Citizens for the United States has adopted unequivocal national policy statements calling for phasing out institutions in lieu of integrated community living arrangements (47). Legislative success in the American states varies inversely with internal interest group conflict. Groups displaying greater agreement among themselves as to fundamental objectives enjoy greater success in creating legislative outcomes favorable to their interests (48). While acknowledging the "useful beginnings" of NAMI chapters, Mechanic (22) has noted that advocates for mentally ill persons are "divided by categories of disorder, by treatment modalities, and by preferences for particular sites of care" (p. 895). Instead of forming common objectives, mental health advocates weaken their impact by competing with one another over "contested terrain" (15). Cromwell et al. (45), representatives of Maryland's chapters of the National Mental Health Association and NAMI and a provider organization, identified the greatest challenge facing the community mental health movement as "building consensus on positions and advocacy strategies, and [acting] with unity" (p. 960).

A third plausible hypothesis regarding differences between the impact of mental retardation and mental health advocacy has to do with the *political implications of stigma*. Chronic mental illness is among the most stigmatizing of disabling conditions—many authorities argue that it is even more stigmatizing than mental retardation (33, 34, 49). Stigma has discouraged relatives of mentally ill persons—and mentally ill persons themselves—from organizing consumer advocacy organizations in the states. Lack of consumer advocacy has prevented the expansion of resources for community mental health services. Approximately 40% of the interviewees in the 10-state survey cited the impact of stigma in mental illness as an inhibiting factor in the expansion of community mental health resources.

A fourth possible factor contributing to the difference in state spending has to do with a basic dissimilarity in the financing of the two community service delivery systems. Third-party reimbursement from private insurance plays a proportionately larger role in financing community mental health services than it does in supporting community mental retardation programs. According to Tischler (50), 28 states have passed statutes since 1978 requiring private health insurers to provide coverage for mental health services. These mandates often shifted payment responsibilities from state mental health agency funds to private third-party sources (51). Because most third-party funds, and also most local funds, were not managed by the state mental health agencies, they were not included in the National Association of State Mental Health Program Directors data set used in this study for comparative analysis.

### *Sources of Community Growth*

The greater quantity of total spending for community mental retardation services in the states was due to the rapid growth of revenue from three sources. Listed in descending order of magnitude, they included state government own-source general revenues, Medicaid Intermediate Care Facilities for the Mentally Retarded funds, and federal Home and Community-Based Services Waiver Medicaid funds. State government own-source general revenue for community mental retardation services grew more than sixfold, from $0.48 billion in fiscal year 1977 to $3.22 billion in fiscal year 1987. This phenomenal 10-year growth pattern reflects the significance of the state legislative appropriations process for community services development and the singular importance of state-level consumer advocacy by groups such as the Association for Retarded Citizens.

Federal policy prohibits mentally ill persons from participating in the program of the Intermediate Care Facilities for the Mentally Retarded. Mentally ill persons between the ages of 22 and 64 are also ineligible to receive Medicaid-funded care in psychiatric hospitals. Hence, the Home and Community-Based Services Waiver Medicaid Program was not available to state mental health agencies for providing Medicaid-funded community services to the majority of adult persons with mental illness in the United States. This is in marked contrast with the mental retardation experience. A representative of the National Association of State Mental Retardation Program Directors recently commented that: "it is difficult to conceive how the states would have been able to expand community-based [mental retardation] services at the rate they have over the past few years in the absence of the waiver program" (40).

As currently structured, Medicaid is unable to cover the costs of care for adult, nonaged mentally ill individuals residing in small residential facilities such as group homes, adult foster homes, and halfway houses, even though extensive coverage for these services may be provided to persons with mental retardation at the option of the states. States do have the option to use Medicaid to cover a variety of important community mental health services ranging from targeted case management to psychosocial rehabilitation. Koyanagi (52), however, recently remarked that "it is impossible to find a single state with a Medicaid services package that provides comprehensive coverage . . . for adults or children" (p. 138). Professionals and advocates must continue to encourage the broadening of state and federal Medicaid coverage for community mental health services (53). Medicaid reform is also an urgent concern in the mental retardation field, but for different reasons: 84% of the more than $6 billion in state and federal funds deployed in 1988 for Medicaid Intermediate Care Facilities for the Mentally Retarded in the United States financed residential services in large congregate care facilities with 16 or more residents (26). The need for Medicaid reform is thus a unifying theme in both the mental health and mental retardation fields today.

### *Need for Systematic Exchange*

Bachrach (35) noted a decade ago that "surprisingly little systematic exchange has taken place between program planners [in mental health and mental retardation] . . . even though there have been remarkable parallels in the aims and purposes of deinstitutionalization for both of these mentally disabled populations" (p. 51). Mental retardation and chronic mental illness are discrete entities diagnostically, but the needs that individuals in both groups have for family-scale supported community living (35) and skills training (54) are unifying features of the two conditions. An important implication of this study is in encouraging comparative state-by-state studies of the expansion of community services for *all* persons with a serious mental disability regardless of the diagnosis. State planning initiatives, studies, and conferences should be jointly sponsored by public and private mental health and mental retardation constituencies such as associations for retarded citizens and NAMI chapters, state developmental disabilities planning councils, the National Institute of Mental Health, and other prominent organizations.

Led by active parent groups, the mental retardation field has established literally thousands of community living arrangements across the country during the past decade. Much remains to be accomplished, however. Many "community-based" placements have been in segregated, large congregate care facilities with too much in common with the state institutions that they are supposed to replace. Staff in community facilities are underpaid and turnover is extremely high (55). Waiting lists in the states for residential services have burgeoned beyond 60,000 persons (56), and more than 50,000 mentally retarded individuals are inappropriately residing in nursing homes (57). Still, a great deal of progress has been made in reconfiguring mental retardation service delivery systems in the states and in developing useful models of supported community living (58). During the 1981–1987 study period, an unprecedented 22 state-operated mental retardation institutions in nine states ceased operations. An additional 15 institutions closed or were scheduled to do so during the 1988–1992 period (59). Several states will be "institution free" by the mid-1990s, which is to say that their mental retardation service systems will be based entirely in community settings (59).

The situation in the mental health field remains, to use APA's terminology (7), a "national crisis" (p. 209). The number of mentally ill persons residing in nursing homes is nearly six times the number of persons with mental retardation residing in these facilities (60). Homeless individuals, about one-third of whom are mentally ill (12), number from 250,000 to 3 million depending on the study cited (61). State hospitals are very expensive to operate, and few states are generous in the allocation of community resources for persons with serious mental illness (16–18).

The mental retardation example of the 1980s has demonstrated that it is possible for the states to implement a substantial expansion of community services to individuals with mental disabilities, and it is possible to do so relatively rapidly. This study has demonstrated empirically that consumer advocacy and civil rights initiatives were important covariates of this dramatic expansion in community mental retardation resources in the states. Santiago (17) was correct in asserting that although the determinants of social reform are multivariate, there must first be "the creation and development of a social movement—a collective incentive of a grass roots nature—defining and guiding the reform" (p. 148). I believe that the decade of the 1990s will be characterized by a continuing aggressive pattern of growth in the allocation of resources for community mental retardation services nationally. A dramatic expansion of resources in community mental health is less certain. Unquestionably, this is long overdue and we must continue to press for its achievement.

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# Cognitive Deficits of Patients With Alzheimer's Disease With and Without Delusions

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*Objective: The goal of this investigation was to study the prevalence of delusions in Alzheimer's disease and to compare the performance of the delusional and nondelusional groups on a neuropsychological test battery. Method: The authors studied 107 patients with Alzheimer's disease and 51 age- and education-comparable normal subjects using a standardized psychiatric interview and a neuropsychological test battery. Results: Thirty-seven patients with Alzheimer's disease had delusions with or without hallucinations. Patients with delusions were significantly more impaired than those without delusions (and the normal comparison group) on the Mini-Mental State examination; Blessed Information-Memory-Concentration Test; Dementia Rating Scale, especially its conceptualization and memory subtests; and a test of verbal fluency. The delusional group also tended to be somewhat more impaired than the nondelusional group on the modified Wisconsin Card Sorting Test and the similarities subtest of the Wechsler Adult Intelligence Scale-revised. Conclusions: Approximately one-third of patients with Alzheimer's disease had developed psychotic symptoms sometime after the onset of dementia. The presence of psychotic symptoms in Alzheimer's disease was associated with greater cognitive impairment, especially frontal/temporal dysfunction, and possibly with a more rapidly progressive dementia.*

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Psychotic symptoms in some form affect a number of patients with Alzheimer's disease at some time during the course (1) of the illness. Reported figures for the prevalence of psychotic symptoms range from a low of 10% (2) to as high as 73% (3). A recent prospective investigation showed that psychotic and other potentially treatable psychiatric symptoms were important risk factors for institutionalization of patients with Alzheimer's disease (4). Modern psychiatric classifications have recognized a variant of Alzheimer's disease with delusions as a distinct subtype (*DSM-III* and *DSM-III-R*). Yet, despite the importance of psychotic symptoms in Alzheimer's disease, there have been relatively few large-scale prospective studies comparing patients with Alzheimer's disease with and without delusions and normal control subjects on demographic and neuropsychological variables. Furthermore, the studies that have been reported have often presented conflicting results. For example, divergent results and conclusions were obtained in six studies (5–11) that compared the degree of cognitive impairment in patients with Alzheimer's disease with psychotic symptoms to that in patients with Alzheimer's disease without psychosis. These studies reported no association (6), a trend toward a negative association (5), a positive correlation (7), or a mixed relationship (8–11) between psychotic symptoms and severity of dementia in Alzheimer's disease. The reasons for the discrepant findings in these studies are unclear. It should be mentioned that all of these investigations relied solely on screening tests for global cognitive impairment, such as the Mini-Mental State examination (12), rather than on more detailed neuropsychological testing.

Evaluating a possible relationship between cognitive deficits and the presence of psychotic symptoms may be important for understanding the pathophysiological basis of delusions and hallucinations in dementia and for early recognition and treatment of these symptoms in patients at different stages of dementia.

Various neurobiological as well as psychodynamic theories have been offered to explain the occurrence of psychotic symptoms in dementia (13, 14). Evidence in favor of each of those hypotheses is rather "soft." There is more evidence supporting limbic, especially hip-

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pocampal-temporal and prefrontal, pathology in "functional" psychoses such as schizophrenia (15–17).

We undertook the present investigation to study the prevalence of delusions in Alzheimer's disease and to compare the performance of delusional and nondelusional groups on a battery of neuropsychological tests. If delusions in Alzheimer's disease are related to hippocampal-temporal or prefrontal pathology, then patients with Alzheimer's disease with delusions may have significantly greater impairment than patients without delusions on tests that are dependent upon the integrity of those brain regions.

## METHOD

### *Subjects*

A total of 107 patients with probable or possible Alzheimer's disease and 51 age- and education-comparable normal subjects participated in this study. (For the purposes of the present study, we excluded normal comparison subjects who had significantly higher levels of education than the patients with Alzheimer's disease). The patients with Alzheimer's disease and the normal comparison group were matched by group means for age (73 and 71 years, respectively) and education (13 years for both). Written informed consent was obtained from all subjects (or their conservators) after the procedures of the study had been fully explained.

The diagnosis of Alzheimer's disease was made independently by two senior staff neurologists at the university's Alzheimer's disease research center according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (18). To reduce the possibility of including subjects with multi-infarct dementias, patients with a score of 4 or greater on the modified Hachinski Ischemia Scale (19) were excluded from the study. Participants with Alzheimer's disease were outpatients residing in the community and were capable of participating in detailed clinical, neuropsychological, and other laboratory evaluations. The patients had not been referred for the evaluation or management of neuropsychiatric or behavioral symptoms. Clinical care remained the responsibility of the primary medical provider. The comparison group of normal subjects consisted of either spouses of patients or volunteers obtained through newspaper advertisements. Subjects with a history of substance abuse, learning disability, or a serious neurological or psychiatric illness were excluded.

### *Procedure*

Each patient and normal comparison subject underwent a comprehensive evaluation at the university's Alzheimer's disease research center. As part of this evaluation, patients received a brief medical examination, a review of medical history including medications and demographic variables, a neurological examination, a psychiatric evaluation, and detailed neuropsychological testing.

*Psychiatric evaluation.* A semistructured interview based on the National Institute of Mental Health Diagnostic Interview Schedule (DIS) for *DSM-III* (20) was performed with each subject and/or the patient's caregiver informant. The DIS permits data collection from all relevant sources, including family members and caregivers, as well as ancillary medical records.

The DIS was administered to subjects and caregivers by experienced nurse practitioners trained in its use. Particular care was taken to distinguish between delusions (fixed and persistent false beliefs) and confabulations (fabrications in response to questions that cannot be answered because of memory loss) (*DSM-III-R*). Psychiatric diagnoses, both before and after the onset of Alzheimer's disease, were assigned by a board-certified psychiatrist (D.V.J.) on the basis of the DIS and other relevant data. The psychiatrist was blind to the subject's neurological diagnosis (i.e., Alzheimer's disease or normal) and neuropsychological test performance.

*Neuropsychological testing.* All of the patients and comparison subjects were evaluated with a battery of neuropsychological tests. The battery consisted of tests of overall mental status: Mini-Mental State examination (12) and Blessed Information-Memory-Concentration Test (21); attention: digit span subtest of the WAIS-R and attention subtest of the Dementia Rating Scale (22); memory: memory subtest of the Dementia Rating Scale; language: an abbreviated form of the Boston Naming Test (i.e., either the odd or even items) (23), Verbal Fluency Test, and the Number Information Test (unpublished 1984 paper of H. Goodglass et al.); problem solving, abstract thinking, and initiation: conceptualization and initiation subtests of the Dementia Rating Scale and the Verbal Fluency Test (24); and constructional ability: block design subtest of WISC-R, Clock Drawing Test, and the Dementia Rating Scale construction subtest.

All of the subjects with a Dementia Rating Scale score above 95 were given a more comprehensive battery that included the following additional neuropsychological tests: Modified Wisconsin Card Sorting Test (25); the similarities, vocabulary, and arithmetic subtests of the WAIS-R; the Visual Reproduction Test (26) of the Wechsler Memory Scale (27); the Buschke Selective Reminding Test (28); and the Trail-Making Test (parts A and B) (29). Of these tests, the Wisconsin Card Sorting Test and the similarities subtest may be most sensitive to frontal lobe dysfunction, while temporal-hippocampal dysfunction may be best assessed by the memory measures of the Buschke Selective Reminding Test and the Visual Reproduction Test.

## RESULTS

Psychiatric evaluation revealed that 37 of the 107 patients with Alzheimer's disease had developed delusions,

**TABLE 1. Psychotic Symptoms in 37 Patients With Alzheimer's Disease**

| Symptom | N[a] |
|---|---|
| Delusions | 37 |
| People stealing or hiding things | 24 |
| People watching or spying | 16 |
| People plotting or trying to hurt or poison | 8 |
| Spouse or another significant person is an impostor | 7 |
| Being followed | 4 |
| Other | 1 |
| Hallucinations | 18 |
| Visual | 13 |
| Auditory | 7 |
| Olfactory | 2 |
| Tactile | 1 |

[a] A number of patients had more than one psychotic symptom.

with or without hallucinations, after the onset of dementia. Thirty of these 37 patients were delusional at the time of their assessment at the Alzheimer's disease research center. The remaining seven patients reported delusions in the past but were free of delusions at the time of their assessment. (These seven patients did not differ significantly from the other 30 on any relevant variable.)

At the time of assessment, nine of the 37 delusional patients were taking a neuroleptic, as were five of the 70 nondelusional patients (usually for treating agitation). Most of these patients were taking low doses of haloperidol (mean dose=1.8 mg per day). With one exception, no patient was taking anticholinergics. None of the patients had any noticeable extrapyramidal reactions, sedation, or confusion at evaluation.

Table 1 describes the types of delusions and hallucinations observed in the patients with Alzheimer's disease and the number of patients manifesting each type. The content of both delusions and hallucinations was usually simple and nonbizarre. The most common delusion, people stealing or hiding things, occurred in 65% of the patients with psychotic symptoms. (These patients had a fixed, firm, and false belief that one or more specific persons had intentionally stolen or hidden their belongings. Demented patients who forgot where they had kept certain things and merely considered a possibility that others might be hiding them were not considered delusional.) Hallucinations were most often visual in nature. They typically consisted of seeing one or more persons (familiar or unfamiliar to the patient).

There were no significant differences between the delusional and nondelusional groups of patients with Alzheimer's disease in mean age, level of education, and duration of illness (table 2). There was a nonsignificantly greater proportion of women in the delusional group (female-to-male ratio=21:16) than in the nondelusional group (female-to-male ratio=35:35). (The ratio of women to men in the normal comparison group was 33 to 18.) None of the patients had a past history of schizophrenia or delusional disorder. There was also no significant association between the presence of psychotic symptoms and the presence of myoclonus or other abnormal movements.

Table 2 presents the mean and median scores achieved by the patients without delusions, patients with delusions, and age- and education-comparable normal subjects on each of the neuropsychological tests given to the entire group of subjects. Group comparisons were performed with the Kruskal-Wallis one-way analysis of variance. All pairwise comparisons were performed with the Mann-Whitney U test. (Nonparametric statistics were preferred because the distribution of values on a number of tests was not normal.) As expected, both Alzheimer's disease patient groups were significantly impaired, relative to the normal comparison group, on all neuropsychological measures (all p values were less than 0.01). The neuropsychological performance was unrelated to current neuroleptic use.

Despite equivalent age, education, and duration of dementia, Alzheimer's patients with delusions performed significantly worse than Alzheimer's patients without delusions on the Mini-Mental State examination (12) ($p< 0.001$), the Blessed Information-Memory-Concentration Test (21) ($p< 0.002$), and the Dementia Rating Scale (22) ($p< 0.04$). The patients with delusions were more impaired than the patients without delusions on two of the Dementia Rating Scale subtests: the conceptualization ($p< 0.04$) and memory ($p< 0.03$) subtests.

The two patient groups performed similarly on the Boston Naming Test (23) and the Number Information Test (unpublished 1984 paper of H. Goodglass et al.). On the test of verbal fluency, patients with delusions generated significantly fewer exemplars from a particular category than did patients without delusions ($p< 0.04$). In contrast, the two groups performed similarly when generating words that begin with a particular letter. There were also no significant differences between the two groups on the WISC-R block design subtest or the Clock Drawing Test.

Figure 1 presents a frequency histogram of percentages of patients with Alzheimer's disease with delusions and those without delusions as a function of the Mini-Mental State examination (12) scores. Whereas almost one-half (47%) of the patients without delusions had Mini-Mental State examination scores higher than 20, less than a quarter (22%) of the delusional patients were in that category. More patients with Alzheimer's disease with delusions had Mini-Mental State examination scores between 11 and 20 (47%) than either above 20 (22%) or below 11 (31%).

The results of additional neuropsychological tests were available for 16 patients with Alzheimer's disease with delusions and 44 patients with Alzheimer's disease without delusions. These revealed no further significant differences between the groups (besides those on tests mentioned earlier for the entire sample of patients). There was, however, a tendency for the delusional patients to be more impaired than the nondelusional group on several tests including the modified Wisconsin Card Sorting Test (25) (means for perseverative errors=10.7, SD=11.5, for the nondelusional group and 13.0, SD=11.2, for the delusional group) and the similarities subtest of the WAIS-R (means=12.7, SD=5.9,

**TABLE 2. Demographic Data and Neuropsychological Test Scores for Alzheimer's Disease Patients Without and With Delusions and Normal Comparison Subjects**

| | Alzheimer's Disease Patients | | | | | | Normal Comparison Subjects (N=51) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Without Delusions (N=70)[a] | | | With Delusions (N=37)[a] | | | | | |
| Item | Mean | SD | Median | Mean | SD | Median | Mean | SD | Median |
| Age (years) | 72.4 | 6.3 | 72.5 | 74.7 | 6.8 | 75.0 | 70.9 | 8.6 | 70.0 |
| Education | 13.5 | 3.5 | 13.0 | 12.9 | 3.3 | 12.0 | 13.0 | 2.2 | 13.0 |
| Duration of dementia (years) | 4.8 | 3.3 | 4.0 | 4.3 | 2.4 | 4.0 | | | |
| Mini-Mental State score[b] | 18.5 | 6.3 | 20.0 | 13.9 | 7.2 | 15.0 | 28.9 | 1.2 | 29.0 |
| Blessed Information-Memory-Concentration Test score[b] | 15.5 | 7.2 | 14.0 | 19.6 | 7.5 | 18.5 | 0.9 | 1.2 | 0.0 |
| Dementia Rating Scale total score[c] | 101.4 | 22.9 | 108.0 | 89.8 | 26.2 | 94.0 | 139.5 | 4.2 | 141.0 |
| Attention subtest | 33.1 | 4.7 | 35.0 | 31.7 | 5.6 | 34.0 | 36.2 | 0.8 | 36.0 |
| Initiation subtest | 21.0 | 7.9 | 23.0 | 18.7 | 9.1 | 20.0 | 36.0 | 2.5 | 37.0 |
| Construction subtest | 4.4 | 1.5 | 5.0 | 3.7 | 1.9 | 4.0 | 5.6 | 0.6 | 6.0 |
| Conceptualization subtest[c] | 29.7 | 7.5 | 32.0 | 25.7 | 8.9 | 28.0 | 37.6 | 2.1 | 39.0 |
| Memory subtest[c] | 12.9 | 5.6 | 13.0 | 10.0 | 4.3 | 10.0 | 24.1 | 1.2 | 25.0 |
| Boston Naming Test | 17.6 | 7.4 | 19.0 | 14.3 | 8.8 | 13.0 | 27.4 | 2.5 | 28.0 |
| Number Information Test score | 13.1 | 6.5 | 14.0 | 12.2 | 7.0 | 14.0 | 21.5 | 2.2 | 22.0 |
| Verbal Fluency Test | | | | | | | | | |
| Letter (FAS) | 18.3 | 10.5 | 17.5 | 16.6 | 12.8 | 13.0 | 41.5 | 13.5 | 40.0 |
| Category (animals, fruits, vegetables)[c] | 16.7 | 9.6 | 16.5 | 12.6 | 10.0 | 10.0 | 47.3 | 9.3 | 48.0 |
| WISC-R block design subtest | 13.5 | 12.1 | 12.0 | 10.2 | 11.6 | 6.0 | 43.1 | 10.0 | 43.0 |
| Clock Drawing Test | 1.6 | 0.9 | 1.0 | 1.3 | 0.7 | 1.0 | 2.8 | 0.4 | 3.0 |

[a] Both of the Alzheimer's disease groups differed significantly from the comparison group on all of the tests listed here ($p<0.01$, Kruskal-Wallis one-way analysis of variance). Neuropsychological test data not available for all Alzheimer's disease patients.

[b] Significant difference between the two Alzheimer's disease groups ($p<0.01$, Mann-Whitney U test).

[c] Significant difference between the two Alzheimer's disease groups ($p<0.05$, Mann-Whitney U test).

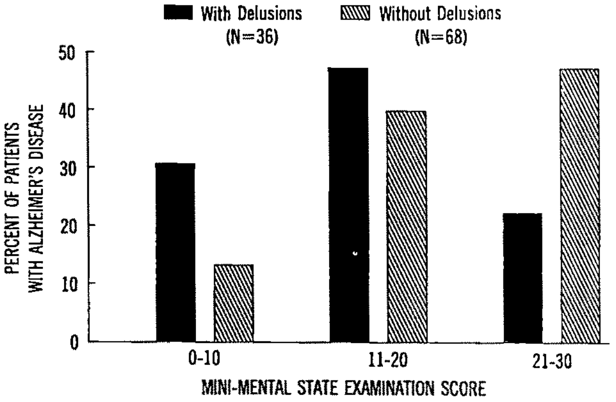
for the nondelusional group and 9.8, SD=6.5, for the delusional group).

## DISCUSSION

Cognitive dysfunction is the hallmark of Alzheimer's disease. Yet, noncognitive behavioral disturbances such as psychotic symptoms are also important from the viewpoint of management of patients with Alzheimer's disease. Surprisingly, the relationship between global cognitive impairment and psychosis in Alzheimer's disease is still not well understood. Even less is known about specific patterns of cognitive impairment associated with psychotic symptoms in Alzheimer's disease. Such information could potentially be helpful in learning about the possible underlying neurobiological basis of psychosis in patients with dementia.

Our finding of a 35% prevalence of delusions and 17% prevalence of hallucinations in patients with Alzheimer's disease is well within the range reported in the literature (1–3). In our study, the presence of psychotic symptoms was associated with a greater severity of dementia, although the delusions and hallucinations were found to be rare in patients with severe dementia.

**FIGURE 1. Distribution of Mini-Mental State Scores Among Patients With Alzheimer's Disease With and Without Delusions**



We should point out that our delusional and nondelusional groups of patients with Alzheimer's disease were similar in terms of duration of dementia, age, and education, and yet the psychotic group had significantly lower Mini-Mental State examination (12) and Dementia Rating Scale (22) scores and higher Blessed Information-Memory-Concentration Test (21) scores, indicating a greater degree of dementia. This suggests a possible association between the occurrence of psychotic symptoms and a more rapidly deteriorating course of dementia. Such a hypothesis would be consistent with the finding of Drevets and Rubin (30), who observed a faster cognitive deterioration in 10 patients with Alzheimer's disease with psychosis than in 15 nonpsychotic patients with Alzheimer's disease. Mayeux et al. (31) and Stern et al. (32) have reported that patients with Alzheimer's disease with both psychosis and a movement disorder have a rapidly progressive dementia. We did not, however, see evidence of a greater frequency of myoclonus or other movement disorders in our psychotic patients.

On neuropsychological testing, the delusional group performed significantly worse than the nondelusional group on a test of memory (the memory subtest of the Dementia Rating Scale [22]) and on two putative tests of frontal function (conceptualization subtest of the Dementia Rating Scale [22] and category subtest of the Verbal Fluency Test). Although the two groups did not differ significantly on the letter fluency task, patients with Alzheimer's disease with delusions performed significantly worse than patients with Alzheimer's disease without delusions on the category fluency. Since category fluency is more dependent than letter fluency upon the integrity of semantic memory (24), this pattern may be indicative of greater disruption in the organization of semantic memory (and greater frontal/temporal dysfunction) in patients with Alzheimer's disease with delusions than in those without delusions. Among patients with higher Dementia Rating Scale scores, the delusional patients with Alzheimer's disease tended to perform worse than nondelusional patients on two putative tests of abstraction, the similarities subtest of the WAIS-R and the modified Wisconsin Card Sorting Test (25); however, these differences did not attain statistical significance. While it would be speculative to draw conclusions about the specific brain localization of these neuropsychological deficits, they are at least consistent with possible frontal/temporal dysfunction. This may have an interesting relationship to the findings of limbic system pathology in schizophrenia—a psychosis characterized by delusions and hallucinations (15–17). Furthermore, Zubenko et al. (33) have recently reported an association between psychosis in Alzheimer's disease and increased densities of senile plaques and neurofibrillary tangles in specific cortical areas, especially the middle frontal cortex and the prosubiculum.

It is possible that psychotic symptoms may have interfered with a patient's performance during neuropsychological testing, creating an erroneous impression of greater cognitive deficits. This explanation is unlikely, however, since none of the patients had such florid psychotic symptoms that they obviously interfered with any of the testing procedures. All of the patients completed the extensive assessment at the Alzheimer's disease research center with excellent cooperation. In addition, the delusional patients did not differ from the nondelusional ones on the attention and initiation subtests of the Dementia Rating Scale (table 2).

The lower prevalence of delusions in severely demented patients could conceivably be an artifact of the patients' deteriorating verbal abilities. Alternatively, the decreased prevalence could mean that a certain amount of neuronal integrity is necessary for the occurrence of delusions. When a patient's language has deteriorated markedly, delusional thoughts cannot be verbally expressed.

A prospective long-term study would be useful in determining whether the development of psychotic symptoms indicates a more rapidly progressive dementia. In addition, functional brain imaging techniques such as positron emission tomography may be helpful in testing for frontal/temporal hypofunction in patients with Alzheimer's disease with delusions.

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# An Empirical Evaluation of the Global Deterioration Scale for Staging Alzheimer's Disease

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*Objective: Although the Global Deterioration Scale has been widely used since its publication in 1982, its stages are based on implicit assumptions about the linearity, temporality, and interdependence of cognitive, functional, and behavioral impairment in Alzheimer's disease. The authors evaluated the validity of these assumptions and tested the hypothesis that psychopathology and functional impairment would occur in earlier stages than the Global Deterioration Scale predicts. Method: The analyses were based on data on 324 patients with Alzheimer's disease who were selected from a registry of such patients. Data analyses included 1) descriptive statistics on the frequency of psychiatric symptoms and difficulties with activities of daily living and 2) logistic regression, with symptoms and functional impairment as independent variables, to test for significant changes in patients' status between stages of the Global Deterioration Scale. Results: More than 50% of the patients at stage 2 displayed psychopathology, and 32% had two or more symptoms. The significant increase in psychiatric symptoms occurred between stages 3 and 4, not between stages 5 and 6 as predicted by the Global Deterioration Scale. Impairment in functional status was observed at all stages, and significant increases occurred between stages 3 and 4 as well as between stages 5 and 6. Conclusions: Psychiatric symptoms and functional impairment occur earlier than predicted by the Global Deterioration Scale, and the rate of change is also different from that specified in the scale. Separate scales to describe cognitive, clinical, and functional status may be the best way to describe the illness until better multidimensional instruments are developed.*

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Alzheimer's disease has been described as an unrelenting "loss of self" (1) characterized by progressive decline of cognitive and functional capacities as well as psychiatric morbidity (*DSM-III-R*, 2). The disease manifests itself in multiple ways, and there is considerable value in developing a scale to describe patients' status. However, limited data are available to document the incidence and prevalence of changes during the course of illness (3, and unpublished work of D. Cohen et al.), and significant variability has been reported in the rate of change in cognitive and noncognitive dysfunction (4–6). Such information is fundamental for the construction of accurate scales for global staging of Alzheimer's disease.

While a number of scales exist, one of the most widely used instruments to stage the course of Alzheimer's disease is the Global Deterioration Scale (7) for primary degenerative dementia. The Global Deterioration Scale is a seven-stage rating scale in which stage 1 reflects no cognitive decline, stage 2 reflects very mild cognitive decline, and stages 3–7 are defined, respectively, as mild, moderate, moderately severe, severe, and very severe cognitive decline. Each stage is associated with clinical phases ranging from normal (stage 1) to late dementia (stage 7), and each is also accompanied by a brief description of clinical characteristics (i.e., functional status, behavioral functioning, psychiatric problems) presumably associated with each stage. Finally, each stage has a diagnostic label: "normal" and "normal aged" for stages 1 and 2, "com-

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patible with incipient Alzheimer's disease" for stage 3, and "mild Alzheimer's disease" to "severe Alzheimer's disease" for stages 4–7.

The Global Deterioration Scale has played an important role in clinical care by focusing attention on the level of patient decline, but the scale itself has significant conceptual and methodological limitations. Reisberg et al. (8) reported that the scale was developed using what they described as "systematic phenomenologic observation" of the nature of symptoms in patients with Alzheimer's disease as well as in other individuals with age-associated memory impairment. There was no clear discussion of the psychometric methods used to relate the seven stages to the clinical parameters specified in the scale. Furthermore, the clinical description for each stage uses different units of observations for behavioral dysfunction. The Global Deterioration Scale is based on implicit assumptions about the linearity, temporality, and interdependencies of cognitive, functional, and behavioral impairment as well as neuroanatomical integrity. These assumptions require empirical evidence to support the Global Deterioration Scale's descriptions of incidence and changes in behavioral dysfunction across the seven stages.

The development of the Global Deterioration Scale relied heavily on correlations between progression on the scale and brain imaging data in a sample of 43 patients and seven other persons who underwent positron emission tomography (PET) scans of their brains (7, 8). In addition, Global Deterioration Scale scores were correlated with several cognitive domains and functional abilities derived from tests with 54 patients and from interviews with 36 patients concerning adaptation.

The Global Deterioration Scale makes predictions about patients' ability to function, as reflected in activities of daily living (e.g., bathing, dressing) and instrumental activities of daily living (e.g., handling money, using a telephone), as well as psychiatric morbidity, on the basis of progressive cognitive loss. In general, the scale postulates that significant functional and psychiatric disability does not occur until the latter stages of dementia. It specifies that psychiatric symptoms such as flattening of affect and anxiety occur in stage 4 and that it is not until stage 6 that pervasive personality and emotional changes occur. Progression of functional impairments is described in the Global Deterioration Scale with uneven detail, but stage 6 is described as the period when some assistance is needed with activities of daily living. The scale states that no assistance with toileting is needed in stage 5 but that patients will have difficulty choosing clothes. In the final stage, patients are described as incontinent of urine, needing assistance with toileting and eating, and losing the ability to walk.

The empirical literature on Alzheimer's disease as well as consensus diagnostic criteria for the disease suggest that psychopathology and functional impairment are prevalent conditions (*DSM-III-R*, 2, 3, 6, and unpublished work of D. Cohen et al.). Therefore, we hypothesized that psychopathology and functional impairment would occur in patients at all stages of the Global Deterioration Scale and that significant differences in adjacent stages would occur before the transition from stage 5 to stage 6 as predicted by Reisberg et al. (7).

**TABLE 1. Ranges of Scores on the Mini-Mental State Examination Used in This Study to Assign Patients With Alzheimer's Disease to Global Deterioration Scale Stages 2–7 and Ranges Used by Reisberg et al. (11)**

| Stage on Global Deterioration Scale | Range of Scores on Mini-Mental State: Reisberg et al. Study | Range of Scores on Mini-Mental State: This Study |
|---|---|---|
| 2 | 25–30 | 26–30 |
| 3 | 20–27 | 21–25 |
| 4 | 16–23 | 17–20 |
| 5 | 10–19 | 11–16 |
| 6 | 0–12 | 1–10 |
| 7 | 0 | 0 |

## METHOD

We used a set of data from a registry of patients with Alzheimer's disease to evaluate the Global Deterioration Scale in a large sample. The data include sociodemographic, clinical, and psychosocial information on dementia patients enrolled at six medical centers in three states between May 1988 and May 1989 (9). The clinical centers enrolled patients 40 years of age or older who were living in the community and who had been diagnosed as having Alzheimer's disease or a related disorder between 1987 and 1989. The Alzheimer's disease patient registry, also known as the Prototype Alzheimer Collaborative Team, was funded as part of a cooperative agreement by the National Institutes of Health and the National Institute on Aging to test the feasibility of enrolling large numbers of patients with dementia at diverse clinical sites in a registry for research on Alzheimer's disease.

The case registration and data collection methods as well as a sociodemographic profile of the entire Prototype Alzheimer Collaborative Team population have been described elsewhere (9). Briefly, a central Data Coordinating and Analysis Center in the School of Public Health at the University of Illinois at Chicago registered patients with Alzheimer's disease and related disorders enrolled at six medical sites in the Miami, Milwaukee, and Chicago areas. The sample for this study included 324 of these patients. Three hundred twenty of them met the *DSM-III-R* or NINCDS-ADRDA (2) criteria for Alzheimer's disease, and an additional four patients were given the diagnosis of primary degenerative dementia according to *DSM-III*. Subjects included in this analysis also had to have no missing data for sociodemographic, psychiatric, mental status, and functional status variables recorded in the case enrollment forms.

Two procedural decisions were made prior to the data analyses for this report. First, we established ranges of nonoverlapping scores on the Mini-Mental State examination (10) as the criteria for defining the seven stages. These ranges, identified in table 1, were modified from

**TABLE 2. Characteristics of 324 Patients With Alzheimer's Disease Classified According to Stages on the Global Deterioration Scale**

| Stage on Global Deterioration Scale | N | Age (years) |  | Sex Ratio (M/F) | Duration of Illness (years)[a] |  |
|---|---|---|---|---|---|---|
|  |  | Mean | SD |  | Mean | SD |
| 2 | 25 | 72.4 | 8.7 | 1.5 | 1.9 | 1.2 |
| 3 | 66 | 73.2 | 7.8 | 0.7 | 3.6 | 3.6 |
| 4 | 68 | 74.1 | 7.6 | 0.5 | 3.4 | 3.0 |
| 5 | 79 | 76.6 | 7.8 | 0.5 | 3.7 | 2.7 |
| 6 | 70 | 75.3 | 6.9 | 0.5 | 4.4 | 2.4 |
| 7 | 16 | 72.8 | 8.6 | 0.7 | 5.4 | 2.0 |
| Total | 324 | 74.6 | 7.8 | 0.5 | 3.7 | 2.9 |

[a] Duration of illness was extracted from the case enrollment form. It indicates time from onset of first symptoms, with documentation of the types of symptoms (e.g., memory, language) and time of diagnosis.

**TABLE 3. Prevalence of Psychiatric Symptoms in 324 Patients With Alzheimer's Disease Classified According to Stages on the Global Deterioration Scale**

| Stage on Global Deterioration Scale | N | Patients With at Least One Symptom |  | Patients With One Symptom |  | Patients With Two or More Symptoms |  |
|---|---|---|---|---|---|---|---|
|  |  | N | % | N | % | N | % |
| 2 | 25 | 13 | 52.0 | 5 | 20.0 | 8 | 32.0 |
| 3 | 66 | 36 | 54.5[a] | 20 | 30.3 | 16 | 24.2[b] |
| 4 | 68 | 48 | 70.6[a] | 11 | 16.2 | 37 | 54.4[b] |
| 5 | 79 | 60 | 75.9 | 15 | 19.0 | 45 | 56.9 |
| 6 | 70 | 54 | 77.1 | 8 | 11.4 | 46 | 65.7 |
| 7 | 16 | 14 | 87.5 | 2 | 12.5 | 12 | 75.0 |

[a] Significant difference between stage 3 and stage 4 ($\chi^2$=4.18, df=1, p=0.04).

[b] Significant difference between stage 3 and stage 4 ($\chi^2$=12.15, df=2, p=0.002).

the overlapping ranges of the Global Deterioration Scale published in 1986 (11). Although Reisberg et al. (11) have argued that mental status scores are not the sole criteria for assignment to the stages of the Global Deterioration Scale, they defined these stages in cognitive terms (7, 8, 11). It was necessary to eliminate overlapping scores to establish the frequency distributions of the noncognitive variables. Second, we chose to examine stages of the Global Deterioration Scale only among Prototype Alzheimer Collaborative Team registry cases in which the patients met diagnostic criteria for probable or possible Alzheimer's disease according to the NINCDS/ADRDA criteria (2), primary degenerative dementia of the Alzheimer type according to *DSM-III-R*, or primary degenerative dementia according to *DSM-III*. Table 2 presents characteristics of the sample classified into stages 2–7, since stage 1 refers to no cognitive decline.

Data analysis consisted of 1) descriptive statistics on the frequency of occurrence of psychiatric morbidity and impairment in the six activities of daily living rated in the Prototype Alzheimer Collaborative Team cases and 2) logistic regression (12), with individual psychiatric symptoms and functional impairment as independent variables, to test for significant changes between stages of the Global Deterioration Scale. For each symptom or impairment category, logistic regression was used to test differences in prevalence between adjacent pairs of stages. If onset of a given symptom is associated with stage k, then the prevalence of that symptom at stage k should be significantly higher than at stage k–1. The differences between adjacent stages 2 through 7 were coded as five indicator variables: $X_3$ was 1 if the stage was 3 or more and 0 if it was otherwise, $X_4$ was 1 if the stage was 4 or more and 0 if it was otherwise, and so on up to $X_7$, which was 1 if the stage was 7 and 0 if it was otherwise. With these five indicator variables as predictors and the logit of symptom or functional impairment status as the outcome, the coefficient $\text{beta}_k$ for $X_k$ is equal to the log odds of prevalence in stage k versus prevalence in stage k–1. If $\text{beta}_k=0$, then the prevalence in stage k is equal to the prevalence in stage k–1. The null hypothesis, $\text{beta}_k=0$, was tested for each coefficient in each model by a chi-square test with one degree of freedom.

## RESULTS

As shown in table 3, 52.0% of the Alzheimer's disease patients at stage 2 displayed psychopathology, and 32.0% had two or more symptoms. By stage 6, 77.1% had psychiatric morbidity, but the significant increase between adjacent levels occurred earlier than postulated by the Global Deterioration Scale, i.e., between stages 3 and 4, not stages 5 and 6.

The results of logistic regression procedures to test significant differences in the prevalence of nine psychiatric symptoms by Global Deterioration Scale stage are reported in table 4. Although patients at all stages displayed agitation, a statistically significant increase in agitation occurred between stages 3 and 4. The prevalence of hallucinations and insomnia also increased significantly between stages 3 and 4.

Impairment in activities of daily living was observed in patients at all stages of the Global Deterioration Scale. Although functional impairments were more severe in later stages, 20% of the patients in stage 2 had at least one impairment in activities of daily living. This doubled to 40% for patients in stage 3 and continued to increase to 51% for those in stage 4, 65% in stage 5, 77% in stage 6, and 100% in stage 7. As shown in table 5, the percentage of patients with difficulties in bathing changed significantly from stage 3 to stage 4 and from stage 5 to stage 6. The most significant change in difficulties in dressing on adjacent stages of the Global Deterioration Scale occurred between stages 4 and 5; however, fully one-fifth of the patients were impaired on this variable in stage 3. The most significant shifts for eating, transferring from bed to chair, and walking occurred between stages 5 and 6 and stages 6 and 7.

TABLE 4. Prevalence of Psychiatric Symptoms in 324 Patients With Alzheimer's Disease Classified According to Stages on the Global Deterioration Scale

| Stage on Global Deterioration Scale | | Agitation | | Apathy | | Behavior Disorder | | Delusions | | Hallucinations | | Paranoia | | Emotional Lability | | Insomnia | | Depression | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| 2 | 25 | 1 | 4.0 | 3 | 12.5 | 1 | 4.0 | 0 | 0 | 2 | 8.0 | 0 | 0 | 3 | 12.0 | 6 | 24.0 | 8 | 7.9 |
| 3 | 66 | 9 | 13.8[a] | 10 | 15.4 | 6 | 9.2 | 0 | 0 | 2 | 3.1[b] | 6 | 9.2 | 2 | 3.1 | 6 | 9.2[c] | 17 | 26.2 |
| 4 | 68 | 26 | 40.0[a] | 14 | 21.5 | 12 | 20.0 | 11 | 16.9 | 10 | 15.4[b] | 13 | 20.0 | 3 | 4.6 | 11 | 21.5[c] | 20 | 26.2 |
| 5 | 79 | 27 | 35.1 | 22 | 28.6 | 19 | 24.7 | 15 | 19.5 | 11 | 14.3 | 10 | 13.0 | 7 | 9.1 | 19 | 24.7 | 27 | 33.8 |
| 6 | 70 | 33 | 47.8 | 17 | 24.6 | 20 | 29.0 | 11 | 15.9 | 14 | 20.3 | 9 | 13.0 | 6 | 8.7 | 11 | 15.9 | 23 | 33.3 |
| 7 | 16 | 10 | 62.5 | 4 | 25.0 | 6 | 37.5 | 2 | 12.5 | 2 | 12.5 | 1 | 6.3 | 3 | 18.8 | 1 | 6.3 | 3 | 18.8 |

[a] Significant difference between stage 3 and stage 4 (beta=1.37; $\chi^2$=9.78, df=1, p=0.002).
[b] Significant difference between stage 3 and stage 4 (beta=1.71;$\chi^2$=4.61, df=1, p=0.03).
[c] Significant difference between stage 3 and stage 4 (beta=1.04; $\chi^2$=4.03, df=1, p=0.04).

TABLE 5. Prevalence of Impairments in Activities of Daily Living in 324 Patients With Alzheimer's Disease Classified According to Stages on the Global Deterioration Scale

| Stage on Global Deterioration Scale | | Bathing | | Dressing | | Eating | | Transfering | | Walking | | Toileting | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % | N | % | N | % |
| 2 | 25 | 1 | 4.2 | 3 | 12.5 | 0 | 0 | 1 | 4.2 | 0 | 0 | 3 | 12.0 |
| 3 | 66 | 8 | 12.5[a] | 14 | 20.8 | 3 | 4.8 | 14 | 21.9 | 9 | 13.8 | 8 | 12.5 |
| 4 | 68 | 24 | 35.2[a] | 21 | 30.5[b] | 8 | 12.5 | 21 | 31.6 | 8 | 12.1 | 13 | 19.6 |
| 5 | 79 | 31 | 38.8[c] | 34 | 42.9[b] | 8 | 10.8[d] | 29 | 37.0[e] | 15 | 19.2[f] | 17 | 21.1[g] |
| 6 | 70 | 41 | 58.5[c] | 39 | 55.9 | 21 | 30.3[d,h] | 27 | 39.1[e,i] | 19 | 27.1[f,j] | 27 | 38.8[g] |
| 7 | 16 | 13 | 81.3 | 16 | 100.0 | 10 | 60.0[h] | 12 | 75.0[i] | 5 | 31.3[j] | 12 | 73.3 |

[a] Significant difference between stage 3 and stage 4 (beta=1.39; $\chi^2$=10.18, df=1, p=0.001).
[b] Significant difference between stage 4 and stage 5 (beta=0.93; $\chi^2$=7.06, df=1, p=0.008).
[c] Significant difference between stage 5 and stage 6 (beta=0.69; $\chi^2$=4.57, df=1, p=0.03).
[d] Significant difference between stage 5 and stage 6 (beta=1.10; $\chi^2$=7.30, df=1, p=0.007).
[e] Significant difference between stage 5 and stage 6 (beta=0.65; $\chi^2$=3.83, df=1, p=0.05).
[f] Significant difference between stage 5 and stage 6 (beta=0.74; $\chi^2$=4.42, df=1, p=0.04).
[g] Significant difference between stage 5 and stage 6 (beta=0.65; $\chi^2$=3.89, df=1, p=0.05).
[h] Significant difference between stage 6 and stage 7 (beta=1.22; $\chi^2$=4.38, df=1, p=0.04).
[i] Significant difference between stage 6 and stage 7 (beta=1.63; $\chi^2$=5.63, df=1, p=0.02).
[j] Significant difference between stage 6 and stage 7 (beta=1.53; $\chi^2$=5.88, df=1, p=0.02).

## DISCUSSION

Since its publication in 1982, the Global Deterioration Scale has been widely used to stage Alzheimer's disease. It was developed by using primarily a conceptual approach, rather than psychometric and statistical methods, to describe cognitive and noncognitive characteristics associated with the course of this disease and related disorders. A number of assumptions were made concerning the occurrence, rate of change, and interrelationships of cognitive impairment, behavioral dysfunction, impairment in activities of daily living, and psychiatric symptoms.

Our results show that significant psychopathology occurs at earlier stages of the Global Deterioration Scale than predicted by Reisberg et al. (7). Although the scale specifically states that no assistance with toileting and eating is needed until stage 6, 21.1% of the patients in stage 5 had problems with toileting and 10.8% had problems with eating. The most significant changes in problems with bathing occurred between stages 3 and 4 as well as between stages 5 and 6. Bathing is not referred to explicitly in the Global Deterioration Scale, but even if it is classified under the general category of "some assistance with activities of daily living" in stage 6, significant change occurred earlier than predicted. Although the Global Deterioration Scale specifically states that no assistance is needed for eating and toileting in stage 5 but is needed in stage 7, these results show an earlier shift.

Our results support one of the basic assumptions underlying the Global Deterioration Scale and all other clinical staging instruments, i.e., that patients with Alzheimer's disease become progressively worse as a natural course of the disease. Indeed, the most useful rating scales for staging Alzheimer's disease rely heavily on cognitive measures (13–15).

It is clear from our results that psychiatric pathology and functional impairment associated with Alzheimer's disease occur sooner than predicted by the Global Deterioration Scale and that the rate of change is different from that specified in the instrument. Our results also have broader implications for understanding Alzheimer's disease. A wide range of psychiatric symptoms may be seen quite early in the disease. Even Alois Alzheimer's initial report (16) described a number of psychiatric symptoms in his 51-year-old patient, including strong feelings of jealousy as the earliest presentation of the disorder. Although cognitive deficits are primary symptoms, they rarely occur without substantial dysfunction in other areas.

The Global Deterioration Scale has been reported to have good interrater reliability, ranging from 0.82 to 0.92 (13, 17, 18). Its validity is difficult to evaluate without prospective longitudinal clinical studies with standardized assessments of the cognitive and noncognitive variables, followed by neuropathological confirmation of the diagnosis of Alzheimer's disease. Validation studies reported to date have relied on correlations of assigned stages of the Global Deterioration Scale with clinical, psychometric, and imaging (i.e., CT and PET scan) variables (7, 8, 17–19). These, however, are indirect measures of validity.

The authors of the Global Deterioration Scale are probably correct in asserting that ordinal progression of functional decline may be affected by coexisting pathology. However, they implicitly postulate a single, relatively consistent progression of decline in Alzheimer's disease without empirically verifying this hypothesis. An example of the difficulties that may occur in the utilization of the scale is the assumption, according to the scale, that symptoms of Alzheimer's disease are not detectable in stage 2 and that stage 3 defines incipient Alzheimer's disease (7, 8, 11, 19). The results in this report demonstrate that patients with clinically diagnosed disease and mild impairment according to the Mini-Mental State examination can be classified in stage 2, and by that stage they already show significant psychopathology.

The use of the Global Deterioration Scale as a global staging instrument carries with it the subtle hazard that because the scaled score provides information in a quasi-mathematical form, it can appear to convey more information about the patient's condition than it actually does. In addition, it presumes the homogeneity of Alzheimer's disease, whereas a growing literature supports the hypothesis that it may be a heterogeneous disease (20–24).

Since staging of Alzheimer's disease by using the Global Deterioration Scale implies an overall clinical state, which in turn is a basis for examining other clinical variables, it is important to recognize that these variables array themselves differently than posited in the Global Deterioration Scale. The use of separate instruments to describe cognitive status, psychiatric symptoms, and functional status (10, 14, 25) may be the most accurate way to describe the illness until better multidimensional scales are developed.

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# Treatment of Imipramine-Resistant Recurrent Depression, IV: A Double-Blind Crossover Study of Tranylcypromine for Anergic Bipolar Depression

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Objective: *Few trials of monoamine oxidase inhibitors (MAOIs) in tricyclic-resistant depression have had double-blind conditions. In the authors' previous double-blind comparison of tranylcypromine and imipramine in anergic bipolar depression, tranylcypromine was significantly more effective. This investigation was a crossover study of nonresponders in the initial study.* Method: *The subjects were 16 outpatients with anergic bipolar depression. Fourteen had not responded to 4 weeks of treatment with at least 30 mg/day of tranylcypromine or 150 mg/day of imipramine, and two patients were crossed over because of intolerable side effects from the initial drug. The crossover medication was prescribed as in the initial double-blind study.* Results: *Twelve patients were crossed over from imipramine to tranylcypromine; nine of them responded to tranylcypromine. Highly significant improvements were documented on the Hamilton, Beck, and Pittsburgh Reversed Vegetative Symptom Scales. Four patients were switched from tranylcypromine to imipramine, but only one responded.* Conclusions: *The high rates of response to tranylcypromine in both the initial and crossover double-blind studies document the efficacy of MAOI treatment for anergic bipolar depression. Moreover, the results further illustrate the utility of MAOIs in tricyclic-resistant depressions.*

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The effectiveness of monoamine oxidase inhibitors (MAOIs) for tricyclic-resistant depressions has been suggested by a number of studies (1–6). Most investigators (1–6) have found response rates of at least 50%, and up to 80% treatment efficacy was found when the MAOI was used in combination with lithium salts (1, 2) or was given to patients who manifested atypical symptoms or reversed neurovegetative signs (5, 6). Despite such apparent consistency across research sites, to our knowledge only one trial using MAOIs for treatment-resistant depression has been conducted under double-blind conditions (5). Thus, it is conceivable that the enthusiasm of the treating clinicians for this rather controversial family of antidepressants may have inflated the response rate. Further, the one published study employing a randomized, double-blind design (5) specifically dealt with nonbipolar patients who had milder, more chronic depression, so its findings may not be generalizable to populations with more episodic or severe illness, such as patients with bipolar affective disorder.

In a previous report (7), we documented that tranylcypromine was significantly more effective than imipramine in a randomized, double-blind study of the acute treatment of 56 patients with anergic bipolar depression. Patients who did not respond to the initial treatment in that protocol were, after an appropriate washout, treated with the other study drug. We now report the results of this double-blind crossover trial.

## METHOD

Both our methods for recruitment and assessment of subjects and the results of double-blind treatment in the initial outpatient study of anergic bipolar depression have been reported elsewhere (7). To briefly summarize, potentially eligible patients were evaluated with the following operationalized criteria (8) for an episode of anergic bipolar depression: 1) bipolar affective disor-

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**TABLE 1. Characteristics of Patients With Anergic Bipolar Depression Who Were Crossed Over From Imipramine to Tranylcypromine (N=12) or From Tranylcypromine to Imipramine (N=4)**

| | | | | | | | | Depression Score Before Crossover | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Drug 1 | | Drug 2 | | | | |
| Initial Drug and Patient | Age (years) | Sex | Bipolar Subtype | Dose (mg/day) | Weeks | Dose (mg/day) | Weeks | Hamilton Depression Scale | Beck Depression Inventory | Reversed Vegetative Symptom Scale |
| Imipramine[a] | | | | | | | | | | |
| 1 | 23 | F | II | 300 | 7 | 30 | 6 | 27 | 42 | 11 |
| 2 | 18 | F | II | 100 | 3 | 30 | 6 | 22 | 29 | 7 |
| 3 | 35 | F | II | 200 | 8 | 50 | 6 | 10 | 12 | 10 |
| 4 | 32 | F | I | 250 | 4 | 60 | 6 | 21 | 44 | 8 |
| 5 | 37 | M | II | 300 | 6 | 50 | 6 | 14 | 15 | 8 |
| 6 | 40 | M | II | 300 | 5 | 40 | 6 | 21 | 17 | 4 |
| 7 | 59 | F | I | 300 | 6 | 30 | 6 | 12 | 16 | 12 |
| 8 | 42 | F | II | 300 | 5 | 50 | 6 | 24 | 38 | 9 |
| 9 | 61 | F | II | 250 | 5 | 30 | 6 | 17 | 17 | 7 |
| 10 | 37 | F | II | 100 | 1 | 20 | 6 | 20 | 19 | 2 |
| 11 | 28 | M | I | 300 | 5 | 40 | 6 | 19 | 22 | 8 |
| 12 | 40 | M | I | 200 | 4 | 40 | 6 | 16 | 20 | 10 |
| Mean | 37.7 | | | 242.0 | 4.9 | 39.2 | 6.0 | 18.6 | 24.3 | 8.0 |
| SD | 12.7 | | | 76.0 | 1.8 | 11.6 | 0.0 | 5.0 | 11.2 | 2.8 |
| Tranylcypromine[b] | | | | | | | | | | |
| 13 | 25 | F | II | 50 | 7 | 250 | 6 | 24 | 43 | 13 |
| 14 | 24 | F | I | 60 | 6 | 100 | 1 | 18 | 26 | 8 |
| 15 | 49 | F | II | 40 | 6 | 100 | 3 | 13 | 11 | 13 |
| 16 | 38 | M | I | 40 | 5 | 150 | 4 | 20 | 29 | 7 |
| Mean | 34.0 | | | 47.5 | 6.0 | 150.0 | 3.5 | 18.8 | 27.3 | 10.3 |
| SD | 11.9 | | | 9.6 | 0.8 | 70.7 | 2.1 | 2.6 | 13.1 | 3.2 |

[a] Eight women and four men; four bipolar I and eight bipolar II.
[b] Three women and one man; two bipolar I and two bipolar II.

der with a current episode of major depression according to the criteria of *DSM-III* and the Research Diagnostic Criteria (RDC) (9), 2) a total score of 15 or higher on the first 17 items of the Hamilton Rating Scale for Depression (10), 3) the clear-cut presence of fatigue and/or volitional inhibition, 4) predominant psychomotor retardation as manifested by a score of 2 or higher on item 8 of the Hamilton scale, and 5) at least one reversed neurovegetative symptom: hypersomnia (1 or more hours of sleep each night beyond normal sleep requirement) and/or weight gain (2.2-kg or greater increase in weight during current episode). We also confirmed the severity of past manic or hypomanic episodes by consulting an independent source (e.g., family member or medical record) to establish the RDC diagnosis of bipolar I or bipolar II subtype. These diagnoses were made with acceptable interrater reliability (7). All patients provided written consent for research participation.

During acute treatment, the patients were seen weekly by a nurse clinician and psychiatrist. All medication capsules appeared identical and contained inert placebo, 10 mg of tranylcypromine, or 50 mg of imipramine. The patients were given two medication containers at each visit: one was labeled "morning medication" (containing either active tranylcypromine or placebo, to be taken at 7:00 and 11:00 a.m.), and the other was labeled "evening medication" (containing either active imipramine or placebo, to be taken at 4:00 p.m. and bedtime). The initial treatment was 20 mg/day of tranylcypromine or 100 mg/day of imipramine. The dose was advanced routinely by one unit of active drug (i.e., 10 mg of tranylcypromine or 50 mg of imipramine) on the 4th day of the protocol. Thereafter, the daily dose was increased by one active drug unit each week until clinical response occurred, up to a maximum dose of six active drug units per day. The treating clinicians decreased the dose or did not increase it at the maximum rate if significant side effects occurred. A patient was considered a nonresponder only if he or she completed at least 4 weeks of treatment and reached at least 30 mg/day of tranylcypromine or 150 mg/day of imipramine.

Depressive symptoms were assessed at each visit with the patient-rated Beck Depression Inventory (11) and the clinician-rated 17-item Hamilton scale, Clinical Global Impression (CGI) (12), and Pittsburgh Reversed Vegetative Symptom Scale (6). The Reversed Vegetative Symptom Scale is an 8-item supplement to the Hamilton scale that measures features of an anergic depressive state (it is available from Dr. Thase on request). It is constructed to correspond exactly with the format of the original Hamilton scale and to explicitly balance the items rating more classically melancholic symptoms with a comparable number of items covering hypersomnia, hyperphagia, and weight gain. In addition, the Reversed Vegetative Symptom Scale provides items covering volitional inhibition, motor retardation, and diurnal mood variation.

After completion of the acute treatment trial, patients

**TABLE 2. Symptomatic Response of 12 Patients With Anergic Bipolar Depression Who Were Crossed Over From Imipramine to Tranylcypromine**

| | Response to Crossover Tranylcypromine Treatment | | | | | | | | | | | Initial Response to Imipramine | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 0 Score | | Week 2 Score | | Week 4 Score | | Week 6 Score | | % Change | | | % Change | | |
| Dependent Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | $t^a$ | Mean | SD | $t^b$ |
| Hamilton Rating Scale for Depression (17-item) | 18.6 | 5.0 | 13.2 | 3.7 | 8.8 | 5.3 | 7.3 | 5.3 | 59.3 | 28.3 | $7.23^c$ | 20.3 | 24.9 | 3.45 |
| Beck Depression Inventory | 24.3 | 11.2 | 18.3 | 9.9 | 14.8 | 11.6 | 12.7 | 9.5 | 47.3 | 29.6 | $5.54^c$ | 19.7 | 23.5 | $2.35^d$ |
| Reversed Vegetative Symptom Scale | 8.0 | 2.8 | 5.3 | 3.2 | 3.7 | 3.5 | 3.8 | 3.7 | 52.5 | 48.8 | $3.22^c$ | 14.5 | 37.8 | 1.79 |

[a] Paired t test (week 0 versus week 6), df=11, one-tailed.
[b] Paired t test (percent change with imipramine versus percent change with tranylcypromine), df=11, one-tailed.
[c] $p< 0.001$.
[d] $p< 0.01$.
[e] $p< 0.05$.

who had failed to meet all three of the following criteria were withdrawn from study medication: 1) CGI score indicating moderate or marked improvement (i.e., +2 or +3), 2) at least a 50% reduction in Hamilton scale score, and 3) Hamilton scale score less than 10. After a 1-week medication-free interval, 14 patients still did not meet these criteria for response and began treatment with the other study medication. Two additional patients were crossed over without having received adequate trials of study medication because they developed severe, intolerable side effects while taking the initial drug. Characteristics of the 16 crossover patients are summarized in table 1. The crossover medication was prescribed exactly as in the original trial. The double blind was maintained throughout this process, and all patients continued to follow a low-tyramine diet.

Upon disclosure of the medications, we found that 10 patients were imipramine nonresponders who had been crossed over to tranylcypromine and only four were tranylcypromine nonresponders who had been switched to imipramine. This discrepancy was due to the greater efficacy of tranylcypromine in the original study (7). Further, both patients who were crossed over because of severe side effects during the initial treatment phase had been taking imipramine. Therefore, the data analysis we had planned was not possible because of the small number of nonresponders crossed over from tranylcypromine to imipramine. The clinical outcome of these four patients treated with imipramine will be summarized descriptively. Improvements during crossover tranylcypromine treatment of the remaining 12 patients on the depression measures (Hamilton scale, Reversed Vegetative Symptom Scale, and Beck scale) were analyzed with paired t tests (i.e., pretreatment score versus posttreatment score). The responses during the initial treatment with imipramine and the subsequent crossover treatment were also compared with paired t tests (i.e., percent change with drug 1 versus percent change with drug 2). Finally, for comparison, the outcome of the 26 patients who received adequate trials of tranylcypromine in the initial study (7) was contrasted with the response of the tranylcypromine crossover group.

## RESULTS

Nine (75%) of the 12 patients who had originally failed to benefit from imipramine responded to tranylcypromine crossover treatment. Two of the three nonresponders during crossover treatment were not able to tolerate tranylcypromine doses higher than 30 mg/day. During the 6 weeks of tranylcypromine crossover treatment, highly significant improvements on all three dependent measures were noted (table 2). The improvements in depression scores during tranylcypromine crossover treatment also were significantly greater than the improvements of these same 12 patients during the preceding imipramine treatment phase. The response to tranylcypromine during crossover treatment also was comparable to the results observed in the 26 patients treated with tranylcypromine in the initial study (7). For example, categorical response was almost identical in the two tranylcypromine treatment groups (75% and 81%), as was percent improvement on the Hamilton scale (t=0.60, df=36, n.s.). Two of the patients who responded to tranylcypromine during crossover treatment developed hypomania during a 12-week continuation treatment period.

Reanalyses of response to tranylcypromine crossover treatment after removal of the two patients who had not tolerated imipramine in the original trial did not alter any of the findings of significance. Of the 10 patients who had received at least 4 weeks of imipramine treatment at doses of 150 mg/day or higher in the initial study, eight (80%) responded to tranylcypromine crossover treatment.

One of the four patients crossed over from tranylcypromine to imipramine responded. Two patients withdrew from treatment prematurely because of side effects, and the remaining patient cycled into a mixed manic state after 4 weeks of therapy with imipramine at 150 mg/day.

## DISCUSSION

In previous "open-label" studies, our group has found that both lithium augmentation (13) and treatment with MAOIs (6) are effective second- and third-line strategies for imipramine-resistant patients with recurrent unipolar depression. In the MAOI study, improvement was most robust in unipolar patients with anergia, psychomotor retardation, and/or reversed neurovegetative features. The current report adds to the literature on tricyclic-resistant depression by documenting the efficacy of MAOI treatment for a group of patients with anergic bipolar depression. Further, to our knowledge, it is only the second trial to use a double-blind, crossover design to study MAOI treatment of tricyclic-resistant depression (cf. McGrath et al. [5]).

Our subjects did not include bipolar patients with more agitated symptoms and were not receiving concurrent lithium therapy. It is conceivable that cotherapy with lithium salts could have enhanced response to imipramine in both the original and crossover protocols, whereas inclusion of patients with agitated depression might have dampened the rate of response to tranylcypromine. Further, it is unclear whether or not anergically depressed, imipramine-resistant patients could have been treated as effectively with a nonsedating tricyclic (e.g., desipramine) or a newer cyclic antidepressant (e.g., bupropion or fluoxetine) as they were with tranylcypromine. Given the inconveniences and risks associated with MAOI treatment, as well as many clinicians' continued preference for tricyclics in the treatment of bipolar depression (14), it seems likely that lithium augmentation will remain a reasonable initial strategy for treatment of tricyclic-resistant bipolar depression. The specific utility of lithium augmentation for psychotic bipolar depression was suggested by the findings of Price et al. (15). Moreover, in the great majority of cases, it is necessary to start lithium treatment after successful antidepressant therapy of bipolar depression.

Nevertheless, it is striking that the response rate and degree of improvement in the current study of imipramine-resistant anergic bipolar patients are so similar to the results of the original study (7). These findings also correspond closely with those from our group's previous open-label study of MAOI treatment of imipramine-resistant patients with unipolar depression (6) and the McGrath et al. crossover study of phenelzine treatment of patients with atypical depression (5). When considered together, the results of these four trials provide compelling evidence that 70%–80% of patients with fatigue, psychomotor retardation, and/or reversed neurovegetative features respond well to MAOIs, even if they first fail to benefit from treatment with standard tricyclics.

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# Lack of Association Between Dopamine $D_1$ and $D_2$ Receptor Genes and Bipolar Affective Disorder

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*Fifty-six patients with bipolar affective disorder and 69 healthy control subjects were tested for association of restriction fragment length polymorphism alleles at the dopamine $D_1$ and $D_2$ receptor loci. No significant associations were found; thus, the hypothesis that a single mutant form of either receptor gene is responsible for the phenotype of patients with bipolar affective disorder was not supported.*

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Human dopaminergic neurons are involved in the control of hormone secretion, voluntary movement, and emotional behavior. These effects are mediated by dopamine $D_1$ and $D_2$ receptors that stimulate and inhibit, respectively, the enzyme adenylate cyclase. Dopamine antagonists display antimanic properties and, conversely, dopaminergic drugs can provoke a switch to mania. Thus, an involvement of dopaminergic receptors in the pathophysiology of bipolar affective disorder would seem evident.

The human $D_1$ and $D_2$ receptor genes have recently been cloned and assigned to the chromosomal regions 5q31–34 and 11q22–23, respectively (1–5). Sometimes chromosomal aberrations provide additional clues to where a gene may reside. In a recently reported family, a balanced 9/11 chromosomal translocation cosegregated with bipolar affective disorder; the breakpoint on chromosome 11 was at 11q22.3 in close proximity to the $D_2$ receptor gene (6).

True association may occur for two reasons: 1) there is strong linkage disequilibrium between a disease-causing locus and the locus under study (recombination fraction <1%), and 2) the marker locus itself contributes to the pathogenesis of the illness (7). In a number of complex disorders, association studies have been successfully performed. In narcolepsy, for example, an almost 100% association with the human lymphocyte antigen (HLA) DR2 allele was found. In affective disorders, studies focused on blood group and HLA antigens; results were either negative or inconsistent. Recent advances in molecular biology and the increasing availability of polymorphic DNA segments as markers have greatly expanded the potential utility of these markers in association studies. Genes that, by evidence of biochemical or pathophysiological abnormalities in the illness under study, possibly contribute to the etiology of the illness serve as candidate genes. Usually, a candidate gene for the disease is selected and a nearby restriction fragment length polymorphism (RFLP) is used as a tool to compare patients and control subjects. The association approach is different from linkage studies, where cosegregation of a marker trait and the disease is examined in families. A major advantage of association studies is that no assumptions have to be made about the mode of inheritance, penetrance, and age at onset of the disease.

Recently, the first association of an RFLP with bipolar affective disorder was reported for the tyrosine hydroxylase gene in patients and control subjects in France (8). However this association could not be replicated in a German sample (9). To look for a possible association between RFLP alleles detected by $D_1$ and $D_2$ DNA probes and bipolar affective disorder, we examined a series of unrelated patients with bipolar illness and a group of control subjects.

## METHOD

We tested 56 patients with bipolar affective disorder ascertained at random from admissions to the Psychiatric Clinic, University of Würzburg, Germany. Thirty-one of the patients were female and 25 were male. All

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**TABLE 1. Dopamine $D_1$ and $D_2$ Receptor Genotypes and Allele Frequencies in Patients With Bipolar Affective Disorder and Healthy Control Subjects**

| | $D_1$ Receptor | | | | | | $D_2$ Receptor | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Genotype[a] | | | Allele Frequency[b] | | Estimated SE | Genotype[c] | | | Allele Frequency[d] | | Estimated SE |
| Group | A1/A1 | A1/A2 | A2/A2 | $a_1$ | $a_2$ | | B1/B1 | B1/B2 | B2/B2 | $b_1$ | $b_2$ | |
| Patients (N=56) | 1 | 13 | 42 | 0.13 | 0.87 | 0.03 | 3 | 17 | 36 | 0.21 | 0.79 | 0.04 |
| Control subjects (N=69) | 1 | 19 | 49 | 0.15 | 0.85 | 0.03 | 5 | 26 | 38 | 0.26 | 0.74 | 0.04 |

[a] A1 allele corresponds to absence of EcoRI restriction site, and A2 to its presence.

[b] $\chi^2$=0.17, df=1, p=0.68.

[c] B1 and B2 refer to absence and presence, respectively, of TaqI restriction site polymorphism.

[d] $\chi^2$=1.05, df=1, p=0.30.

suffered from bipolar disorder that had been diagnosed according to the *DSM-III* criteria. Diagnostic assessments were based on clinical interviews by an experienced psychiatrist, review of case notes, and family history data. Twenty-nine patients had family histories of affective disorder.

Sixty-nine persons were tested as control probands. They were recruited from among medical students and laboratory staff members. Persons with family histories of psychiatric illness were excluded. The female-to-male ratio in this group was 34:35.

All subjects examined (patients and control subjects) were native Germans. All gave informed consent.

Venous blood samples, with EDTA as the anticoagulant, were drawn from all probands. Genomic DNA was extracted from buffy coat preparations by salting out with saturated sodium chloride solution and then digested with restriction enzymes. DNA fragments were subjected to electrophoresis on 0.7% agarose gel and transferred to nylon filters. DNA probes were labeled with $[\alpha\text{-}^{32}\text{P}]$dCTP by the random primer method and hybridized to the blots. Filters were washed at a final stringency of 0.1×standard saline citrate at 65 °C and exposed to Kodak XAR-5 film with image intensifier for 1–4 days at –70 °C to produce autoradiographs.

A 3-kilobase (kb) fragment of a human $D_1$ DNA clone containing on a single exon the entire coding region of the $D_1$ receptor detects a 6.8-kb and a 10.5-kb band RFLP in EcoRI digests. An 18-kb fragment of a human $D_2$ DNA clone detects a 2.2-kb and a 9.0-kb band RFLP in TaqI digests. This fragment comprises the sequence coding the 63 amino acid residues of the C terminus of the $D_2$ receptor, the 3′ untranslated region of the receptor mRNA, and 3′ flanking sequences.

## RESULTS AND DISCUSSION

To test for the general involvement of the dopamine $D_1$ and $D_2$ receptor genes in bipolar affective disorder, we determined RFLP genotypes in the patients and the control subjects. Genotypic frequencies were not found to differ significantly from those expected according to the Hardy-Weinberg equilibrium (10).

When the allele frequencies of the two test groups were compared, there were no significant associations between affected status and allele frequencies at the two dopamine receptor loci (table 1). The allele frequencies in both of the groups were similar to those reported for unrelated healthy Caucasians (2, 5). For the EcoRI site, the comparison between patients and control subjects, expressed as a relative risk, was 1.16 (p=0.68). The relative risk for the TaqI site was 1.37 (p=0.30). To demonstrate the power of the study under the given sample size, we included a power calculation. Fixing the allele frequencies for the control subjects at 0.15 for the A1 allele of the $D_1$ receptor RFLP and at 0.26 for the B1 allele of $D_2$, the power to detect an association is >0.80 for allele $a_1$ frequencies$\leq$0.04 ($b_1\leq$0.12) and $a_1$ frequencies$\geq$0.30 ($b_1\geq$0.43) in the patient group.

Since the genetic load may be higher in patients with family histories of affective disorder, we subdivided the patient group on the basis of having no relative with affective disorder (N=27) or at least one relative with affective disorder (N=29). The allele frequencies of the two dopamine receptor RFLPs for these two groups of bipolar patients were compared to the frequencies in the control group (data not shown). No significant differences between the two patient groups and the control group were found.

The results of this study do not support the hypothesis that a single mutant form of either the dopamine $D_1$ or the dopamine $D_2$ receptor gene is responsible for the phenotype of all or an appreciable proportion of patients from the general population who are suffering from bipolar affective disorder.

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# Controlled Investigation of the Amobarbital Interview for Catatonic Mutism

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*Objective: Clinical reports over the last 60 years suggest that the amobarbital interview is effective in relieving catatonic symptoms. This has never been substantiated with methodologically sound trials. The authors postulated that a randomized blind comparison of intravenous amobarbital and saline would demonstrate the superiority of amobarbital in relieving catatonic mutism. Method: The subjects were 20 inpatients with catatonic mutism. They were randomly assigned to either saline (N=10) or a 5% amobarbital solution (N=10), and the infusions were administered intravenously at a rate of 1 cc/min or less over 10 minutes by a blinded physician. A second blinded physician administered a semistructured interview during the infusion to control for the effect of suggestion. A third blinded physician rated patient responsiveness, reactivity, and arousal. Any patient who was unresponsive to the initial infusion was crossed over to the other infusion. Interviews were videotaped for determination of interrater reliability. Results: In the initial infusions, six of 10 patients responded to amobarbital and zero of 10 responded to saline. Four of the saline nonresponders responded when given amobarbital. Response was evident by the 4th minute of the amobarbital infusion. Interrater reliability was high. The responders and nonresponders differed significantly in the variance of the weight-adjusted amobarbital dose, and the responders tended to be older and female. Conclusions: Intravenous amobarbital is superior to saline in relieving catatonic mutism, although only 50% of these patients responded. The nonresponders were distinguished from the responders by a greater variance in the weight-adjusted dose of amobarbital.*

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Sixty years ago Bleckwenn (1, 2) proposed the administration of intravenous amobarbital as a means of relieving acute symptoms in psychiatric patients. Since that time amobarbital-facilitated interviews have become popularly known as "Amytal interviews" (2) and have been credited with the power to assist in retrieval of repressed memories (anamnesis), production of blocked affects (abreaction), and the relief of conversion and catatonic physical symptoms (3). To our knowledge, however, no randomized and blinded studies have substantiated the superiority of amobarbital over a control solution.

Two studies using a saline control (4, 5) strongly suggested that amobarbital is superior in relieving catatonic symptoms, but these studies did not use random assignment or blindly made ratings. The only blinded, randomized, and controlled study of the amobarbital interview in psychotic and severely disturbed patients (6) failed to show that amobarbital is more effective than a control solution in revealing new symptoms or clarifying the differential diagnosis. A series of methodologically sound investigations in "psychoneurotic" patients (7) also failed to establish the superiority of amobarbital in producing anamnesis/abreaction.

We conducted a randomized, blinded, and controlled investigation of the amobarbital interview with catatonic patients. We hypothesized that intravenous amobarbital would be superior to saline in relieving catatonic mutism. Mutism was chosen as a target symptom because 1) it is among the most frequent of catatonic signs (8), 2) we felt it could be reliably identified by independent examiners, 3) previous anecdotal reports (4) suggested that mutism is the catatonic symptom least vulnerable to placebo response, and 4) because of the variable presentations of catatonia, we felt it was

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important to homogenize our study group with one unifying symptom.

## METHOD

### *Subjects*

Of the 30 patients screened for this study, 10 were mute at the time of admission but became at least partially verbal on the wards or during preparation for the amobarbital interview, so they were not included in the study. Twenty patients completed the study. Their mean age was 45.4 years (SD=15.4), and there were 10 men and 10 women. All were inpatients and were persistently and totally mute; none of the patients made intelligible verbal or nonverbal responses or movements. For 18 patients, mutism was an acute symptom that was present at admission and had lasted 1–5 days, and these patients participated in the study during the first week of hospitalization. The other two patients had been mute and hospitalized for 4–6 months. Sixteen of the patients were identified and studied at a state psychiatric hospital, and the other four patients were identified at a university hospital. Admission diagnosis was not considered in selecting patients for the study; we required only catatonic mutism.

Acute mutism may be related to neurological or psychiatric conditions (9). Even among psychiatric conditions, mutism does not necessarily indicate catatonia, so, in addition to mutism, we required other signs of catatonia. All of the patients were in a motionless stupor. Twelve demonstrated rigidity, eight were negativistic, and one had catalepsy. None of the patients had a prior documented episode of catatonia. Catatonic symptoms can be evanescent, so, to reduce the possibility of placebo response, we required that our subjects demonstrate persistent mutism. Persistent mutism was defined as being 1) noted in the admission mental status examination, 2) still present when the patient was screened by one of us in the first week and consistently documented in the progress notes, 3) still present when the patient was taken to a distant examination room and an intravenous line was inserted.

Each patient was examined by a neurologist at the time of the interview (W.M.M.) and was found to be free of localizing neurologic signs. No patient had a history of head trauma, epilepsy, or other primary brain disease. Ten patients underwent routine EEGs before the amobarbital interview, and all EEG results were nonsignificant.

### *Consent*

Informed consent was obtained from the guardians of the four patients who had previously been judged incompetent in legal proceedings. The remaining patients were unable to give consent by virtue of their illness. This issue has been recently addressed in similar circumstances (10). In our study, the investigational review board of the university hospital required a relative's consent for the procedure. A second consent for use of the acquired data was obtained from the patient later, when competency had been regained with treatment.

### *Procedure*

Each patient was taken to a private area of the hospital, and an intravenous line was inserted in the patient's arm. The presence of catatonic mutism was again confirmed by two psychiatrists (W.V.M., F.E.S.). A psychiatrist (F.E.S.) made baseline recordings of the patient's level of awareness and cooperation. A second psychiatrist (W.V.M.) conducted the interview, and a third physician (W.M.M.) administered the intravenous infusion. A nurse prepared a 10-cc syringe of 5% amobarbital (which is indistinguishable from saline). A syringe containing either saline or amobarbital solution was given to the first three physicians, who remained blind to the identity of the solution. The nonblind nurse left the room and did not participate in any aspect of amobarbital administration, interviewing, or patient ratings. A counterbalanced design allowed for 10 patients to initially receive amobarbital and 10 to receive saline. We followed Bleckwenn's original protocol of giving no more than 1 cc/min (1, 2). The physician administering the infusion was encouraged to give 1 cc/min unless the patient was obviously showing a beneficial response or was going to sleep. The exact rate of infusion, however, was at the discretion of the physician administering the solution. Each infusion was given over 10 minutes.

During a clinical amobarbital interview, the physician generally gives the patient suggestions and encouragement. These factors could be more important than the amobarbital in relieving catatonic mutism, so we used a semistructured interview created for this study. The interview consisted of 10 statements of assurance and questions about orientation that were made to each patient during each 10-minute infusion at a tempo determined by the interviewer (appendix 1). The interviewer was allowed to break away from the semistructured interview if the patient responded to a particular line of questioning.

The physician rater assessed the patient's level of arousal and reactivity during each minute of the infusion by using a 5-point scale created for this study (appendix 2). Also, at the end of the 10-minute infusion the rater judged each patient's global response to the infusion on a 5-point improvement scale (appendix 3). All ratings were performed by the same rater. Only patients judged to have a "definite and sustained" or "dramatic" improvement were deemed "responders." Patients with equivocal or transient changes were designated "nonresponders."

At the end of the first 10-minute infusion, any patient who had failed to respond was immediately given another interview with whichever solution was not given in the first infusion. Because no patient responded to saline, every patient thus received amobarbital. As dur-

**TABLE 1. Characteristics of Patients With Catatonic Mutism Who Did or Did Not Respond to Amobarbital Interviews**

| | Age (years) | | Sex | | Affective Disorders | | Body Weight (kg) | | Amobarbital Dose | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Total (mg) | | Weight-Adjusted (mg/kg) | | |
| Group | Mean | SD | M | F | Yes | No | Mean | SD | Mean | SD | Mean | SD | Variance[a] |
| Responders (N=10) | 51.6 | 15.9 | 4 | 6 | 7 | 3 | 63 | 15 | 305 | 91 | 4.9 | 1.2 | 1.3 |
| Nonresponders (N=10) | 39.3 | 12.9 | 6 | 4 | 5 | 5 | 74 | 22 | 355 | 152 | 4.6 | 2.3 | 5.4 |
| Total (N=20) | 45.4 | 15.4 | 10 | 10 | 12 | 8 | 70 | 17 | 330 | 125 | 4.8 | 1.8 | 3.2 |

[a] t=4.1, df=18, p<0.03.

ing the first interview, ratings were systematically carried out every minute and at the end of 10 minutes. The interviewer again used the semistructured interview. The patient's weight, the psychotropic drugs administered over the previous 24 hours, the total dose of amobarbital given, and the discharge diagnosis were recorded.

### *Videotaping and Reliability*

We videotaped the interviews to test interrater reliability of global improvement ratings. Twelve patients allowed their videotapes to be retained, and 11 of these tapes were of sufficiently good technical quality to permit review. Each videotape was reviewed blindly by an author in a different site; a state hospital tape was reviewed by a university hospital staff member, and vice versa. On the basis of global improvement at the end of the 10-minute infusion, each patient was categorized as either "responder" or "nonresponder" according to the previously stated criteria.

### *Statistics*

Patient age, weight, drug doses, and ratings are presented as means and standard deviations. The proportions of responders and nonresponders in the amobarbital and placebo conditions were compared by using Fisher's exact test. The magnitude of change in the arousal rating of the responders was tested with a two-tailed signed ranks test. The contributions of gender, medication status, and discharge diagnosis to response were assessed with Fisher's exact test. The contributions of age, weight, total dose of amobarbital, and weight-adjusted dose of amobarbital to response were assessed with two-tailed t tests for unpaired data. The reliability of our blinded videotaped ratings of responder status was tested with a phi correlation for dichotomous variables. The phi coefficient was then converted to a chi-square for significance testing.

## RESULTS

Six of the 10 patients randomly assigned to receive amobarbital were judged responders, whereas none of the 10 assigned to saline responded (p=0.005, Fisher's exact test). Of the four nonresponders to amobarbital, none responded to the follow-up interview with saline. By contrast, four of the initial nonresponders to saline became responders when blindly crossed to the amobarbital follow-up. Therefore, eventually 10 (50%) of the 20 patients responded to amobarbital, and none responded to saline.

Of the 11 patients whose videotapes were reviewed, six had been judged responders when given amobarbital interviews, and five were nonresponders. All 11 were identically classified by the raters of the videotapes (phi=1.00, $\chi^2$=12, df=1, p<0.001).

The baseline mean arousal rating for the 10 responders was 1.9 (SD=0.6). By the 4th minute of the amobarbital infusion, the score was 3.3 (SD=0.7), which was a significant improvement (p<0.02). Improvement in the arousal score continued through the 10th minute (mean=4.3, SD=0.8; p<0.002). The nonresponders showed no significant change in arousal ratings between baseline and the 10th minute (mean=2.3, SD=0.9, versus mean=2.1, SD=1.0).

There were no significant differences between responders and nonresponders in age, gender, affective versus nonaffective diagnosis, medication status in the previous 24 hours, weight, total dose of amobarbital, or mean dose of amobarbital in milligrams per kilogram of body weight. There was, however, significantly greater variance in the weight-adjusted amobarbital dose in nonresponders than responders (table 1).

After the amobarbital interview the choice of treatment was at the attending physician's discretion. A review of the discharge summaries produced the following final diagnoses: schizophrenia (N=6), unipolar depression (N=5), bipolar depression (N=4), mania (N=3), brief reactive psychosis (N=1), and dementia (N=1).

## DISCUSSION

To our knowledge, this study is the first to demonstrate the superiority of intravenous amobarbital over placebo in relieving a psychiatric symptom. Some clinicians now prefer to use benzodiazepines in relieving catatonic symptoms (11–13), but we felt that an investigation of amobarbital was indicated because it remains the historic "gold standard" and the basis of a rich clinical literature. Although this study focused on catatonic mutism, the literature suggests other catatonic symptoms would be equally responsive (14). Intravenous saline with our semistructured interview was completely ineffective in relieving catatonic mutism. This suggests that some change in the patient's physiology must occur to dispel catatonic mutism in the brief time of our interview. Even so, only 50% of our 20 patients responded to amobarbital. The responders showed signs of improvement by the 4th minute. The 100% concordance of our videotape-based reliability ratings of responders may seem surprisingly high, but "definite and sustained" improvement in our target symptom of mutism was easy to identify. Many of our nonresponders had partial or unsustained improvements in mutism, and by strictly defining our criteria for response we improved our reliability while losing some sensitivity to response.

Few identifiable differences separated responders from nonresponders. Although the responders had a higher mean age and higher prevalences of female sex and mood disorders, there were no significant differences in age, gender, diagnosis, weight, medication status, total dose of amobarbital, or weight-adjusted dose. Our small number of subjects may have limited our power to discern significant differences between responders and nonresponders. The variance in the weight-adjusted dose of amobarbital was significantly greater in the nonresponders. Some nonresponders fell asleep with as little as 100 mg of amobarbital, whereas others received 500 mg without effect. Although it is possible that greater flexibility in our dosing protocol might have resulted in a higher response rate, it is equally likely that patient factors accounted for the large variation in sensitivity in the nonresponders. Among the subjects studied by Elkes (5), the degree of response of catatonic patients to intravenous amobarbital was relatively fixed for each patient: "Higher doses did not lead to an increase in accessibility, but would merely result in sleep." Although we agree with Elkes that patient factors may limit the degree of patient responsiveness, we believe that the degree of responsiveness could change from one catatonic episode to another within the same patient. We have had the opportunity to administer multiple amobarbital interviews separated by months to patients with recurrent episodes of catatonia and have found that some patients respond during one interview but not the next.

Whether the response of catatonic mutism to intravenous amobarbital implicates a specific neurochemical pathophysiology is open to debate. Amobarbital, like other barbiturates, probably has a GABA-ergic agonist effect (15). Benzodiazepines and ECT also relieve catatonia and may exert their therapeutic effects through GABA-ergic pathways (16–18). On the other hand, we have seen catatonia relieved in 1 to 2 days with intramuscular neuroleptics or intramuscular amitriptyline. Also, studies published decades ago (19, 20) showed sudden relief of catatonia with inhalation of 30% carbon dioxide or subcoma doses of intramuscular insulin. We suggest that although a change in the patient's physiology is necessary to relieve catatonia, the type of physiologic change may be varied.

The risk-benefit ratio of performing an amobarbital interview is favorable. We have had no untoward events in our experience with amobarbital in catatonia. Benzodiazepines may be as effective and perhaps safer, but no controlled trials exist to our knowledge. In summary, intravenous amobarbital was superior to saline in relieving catatonic mutism during a brief interview. Nevertheless, only 50% of our patients responded. The amobarbital interview is useful, low risk, and inexpensive with the proper technique.

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**APPENDIX 1. Statements/Questions in Semistructured Amobarbital Interview (given in any order, depending on interview flow)**

1. What is your name (age, or residence)?
2. Why are you here?
3. Do you know where you are?

4. Why are you not talking?
5. Are you uncomfortable?
6. We are giving you medicine in your vein that may let you tell us what is wrong.
7. We are going to take care of you here.
8. You may be feeling relaxed; that is a good sign.
9. This is a safe place to talk.
10. We want to help you and hear about your worries.

**APPENDIX 2. Scale for Rating Arousal and Reactivity During Amobarbital Interview**

1. No meaningful response to questioning or tactile stimulation; appears stuporous.
2. Interrupted or semipurposeful response to questioning or tactile stimuli; appears stuporous.
3. Makes meaningful response to questioning or tactile stimuli, but no spontaneous or voluntary communication.
4. Spontaneous or voluntary communication, but patient appears asleep or unmoving.
5. Spontaneous or voluntary communication, and the patient appears awake with spontaneous movements.

**APPENDIX 3. Scale for Rating Clinical Global Improvement at End of 10-Minute Amobarbital Interview**

Compared with baseline this patient is now . . .
1. Clinically worse.
2. Clinically unchanged.
3. Mildly or transiently improved.
4. Showing definite and sustained improvement.
5. Dramatically improved.

# The Role of Violence in Decisions About Hospitalization From the Psychiatric Emergency Room

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*Objective: The authors evaluated the relationship between violent behavior and decision making about hospitalization from the psychiatric emergency room. Method: The medical charts of 321 patients evaluated in an urban psychiatric emergency room during a 4-week period were reviewed retrospectively. Violent behavior was defined as physical attacks on persons or fear-inducing behavior before or during the evaluation in the emergency room; and its value in predicting hospitalization decisions was assessed with logistic regression analyses that also included 12 demographic, clinical, and contextual variables. Results: A model predicting hospitalization decisions was developed and cross-validated. Although violent patients were more likely to be hospitalized than nonviolent patients, clinical variables such as diagnosis and overall severity of psychiatric impairment were more important than violent behavior in predicting hospitalization decisions. Conclusions: Despite legal pressures to focus on overt behaviors such as violence as a basis for liability prevention and civil commitment, clinicians in this study did not allocate inpatient resources to preventively detain persons unlikely to benefit from treatment. Rather, they hospitalized the most severely disturbed patients, with diagnoses such as schizophrenic and manic disorders for which a widely accepted therapeutic armamentarium exists. The results are consistent with clinical recommendations that in the evaluation of the violent patient, attention needs to be given to the underlying disorder, since violent behavior itself can result from diverse causes only some of which require inpatient psychiatric treatment.*

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The urban psychiatric emergency service has become a major point of entry to inpatient treatment for the severely mentally ill (1, 2). A large subgroup of patients who come to psychiatric emergency services have been recently violent (3, 4). Although clinically oriented criteria for decision making about hospitalizing violent patients have been proposed (5), there is controversy about whether legal considerations have unduly influenced clinical decisions about hospitalizing violent patients. Some have suggested that legal developments, such as the widespread adoption of dangerousness as a standard for civil commitment and the creation of a legal duty to protect the potential victims of patients' violence, have resulted in the use of hospitalization for preventive detention of violent patients who are unlikely to benefit from treatment (6, 7). However, research about the relationship between violence and referral from the psychiatric emergency room for hospital admission is limited. That is, while violence has been correlated with the decision to hospitalize (8), previous studies typically have not evaluated the relationship between violence and hospitalization in the context of patients' other clinical characteristics, such as level and type of psychopathology. The present study will provide information about this topic by evaluating the relationship between violence and hospitalization decisions while taking into account other clinical characteristics which have also been associated with hospitalization decisions.

Previous research on the decision to hospitalize patients from the psychiatric emergency room has often yielded conflicting results. Several studies have identified demographic, clinical, and contextual variables that are associated with hospitalization decisions. Demographic predictors have included age (9), gender (10),

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ethnicity (11), and employment status (12). Contextual variables such as family supports (13) and referral source (14) have also been correlated with hospitalization decisions. However, clinical variables such as diagnosis, symptoms, and indications of dangerousness to self and others have been more consistently associated with hospital admission (8, 15). Part of the reason for the conflicting results of previous studies may have been a failure to consider the intercorrelations between variables associated with hospitalization decisions and failure to cross-validate predictive models (15). The present study will improve on the design of most previous studies by using multivariate methods that take into account the intercorrelations between variables and will cross-validate models predicting hospitalization based on these variables. In this way the influence of violent behavior on hospitalization decisions is expected to be evaluated in a relatively reliable fashion.

This study addressed three specific questions: 1) What demographic, clinical, and contextual variables are associated with hospitalization decisions in a large, urban psychiatric emergency room? 2) What is the relationship between violent behavior, before or during the initial evaluation in the psychiatric emergency room, and referral for hospitalization? and 3) How useful is knowledge that a patient has been recently violent in predicting hospitalization decisions when other correlates of hospital referral are taken into account?

## METHOD

### *Procedure*

The study was conducted in the psychiatric emergency service of a university-affiliated hospital funded to serve the city and county of San Francisco. The sample included all patients evaluated in the psychiatric emergency service during a 4-week period in August 1988. If a patient had more than one visit to the psychiatric emergency service during the study period, only the first visit was included. The final sample consisted of 321 unduplicated patients.

The patients' charts were reviewed retrospectively to determine whether or not they were referred for inpatient psychiatric admission from the psychiatric emergency service, as well as for a number of demographic, contextual, and clinical variables that previous research has suggested are associated with hospitalization decisions. Demographic variables included gender, age, ethnic background, and employment status. Contextual variables included referral source and whether or not the patient lived with family. Clinical variables included primary psychiatric diagnosis, based on the *DSM-III-R;* overall severity of psychiatric impairment at the time of admission to the psychiatric emergency service, based on the treating clinician's rating on the Global Assessment Scale (GAS) (16), a widely used measure that has been shown to have good reliability and validity (16–17); a rating by the treating clinician of whether or not drug or alcohol problems were present; and the extent of recent suicidal behavior. Suicidal behavior was rated on the Longitudinal Inventory of Function and Encounters developed by Hargreaves, LeGoullon, and Gaynor in 1983. The rating of suicidal behavior on this scale ranges between none, threat, gesture, and attempt. The reliability and validity of the Longitudinal Inventory of Function and Encounters have been documented in previous research (18–20). The charts also were evaluated for the presence or absence of violent behavior during the two weeks before admission to the psychiatric emergency service, based on a modification, used in several previous studies (21–23), of a rating form developed by Lagos et al. (24), which includes three levels of increasingly severe violence: no violence, fear-inducing behavior (i.e., verbal attacks, threats to attack persons, and attacks on objects), and physical attacks on persons. If a chart indicated that more than one type of violence had occurred, only the most serious type was retained. We also evaluated the presence or absence of violent behavior during the first 24 hours that the patient was in the psychiatric emergency service. The ratings were made by experienced clinical staff who completed training in the coding system to a criterion interrater reliability (25) of kappa=0.75 before starting the chart reviews.

### *Data Analysis*

To describe the demographic, clinical, and contextual variables associated with hospitalization decisions, we first examined the relationship between each patient characteristic separately, using chi-square analyses, corrected for continuity when appropriate. A similar strategy was employed to describe the relationship of violent behavior to hospitalization decisions.

To assess how useful information about violent behavior was in predicting hospitalization decisions when other correlates of hospital referral are taken into account, we used logistic regression methodology. This approach combines information from several patient characteristics to yield a prediction of whether or not the patient will be hospitalized. Following the method described by Mosteller and Tukey (26), we included in each model variables that previous research has consistently found to predict hospitalization decisions (i.e., preadmission violence, suicidal behavior, primary diagnosis, and level of functioning as indicated by GAS score). Next, variables that have received some support in the literature as being important to hospitalization decisions (e.g., presence of concomitant drug and alcohol problems and presence of assaultive or fear-inducing behavior in the psychiatric emergency service) were added to the model, which was then subjected to a backward elimination procedure whereby variables that did not contribute significantly ($p<0.05$) to the classification of whether or not patients were hospitalized were removed from the model. Finally, variables that have received only inconsistent support in the literature as determinants of hospitalization (e.g., ethnicity, gender, living with family, referral source, and employment status) were subjected to a forward selection procedure, whereby they were added to the model if their inclusion resulted in a significant ($p<0.05$) increase in the ability of the model to predict hospitalization decisions.

To permit later cross-validation analyses, we first developed the prediction model on a subset of two-thirds of the patients that had been selected randomly with stratification on these variables: diagnosis, violent behavior, suicidal behavior, and GAS score. Then, we cross-validated the model by applying it to the remaining one-third of the patients and assessing how accurately the patients were classified as to hospitalization decisions.

## RESULTS

### *Characteristics Associated With Hospitalization*

Thirty-nine percent (N=124) of the 321 patients were referred for psychiatric hospitalization after evaluation in the psychiatric emergency service; 19% (N=60) were referred to outpatient treatment, day treatment, or community residential treatment such as halfway houses; 11% (N=36) were referred to drug or alcohol treatment programs; 12% (N=39) were referred for inpatient medical (nonpsychiatric) treatment; and 19% (N=62) had other dispositions, such as other social service or legal referrals and patient refused referral. As shown in table 1, patients were significantly more likely to be hospitalized if they were male and if they were unemployed. However, other demographic and contextual variables such as age, ethnic background, referral source, and residing with family did not have a statistically significant association with hospitalization decisions. Table 2 shows that patients' clinical characteristics were more closely associated with decisions about hospitalization. Patients with a primary diagnosis of schizophrenia were significantly more likely to be hospitalized, whereas patients with substance abuse disorders were less likely to be hospitalized. Similarly, patients with more severe overall psychiatric impairment, as indicated by lower ratings on the Global Assessment Scale, were more likely to be hospitalized. Interestingly, patients with a recent history of suicidal behavior were underrepresented in the group of patients referred for inpatient treatment. Although violent behavior in the psychiatric emergency service was not significantly associated with hospitalization, there was a marginally significant trend for preadmission violence to be associated with referral for hospitalization. Similarly, there was a trend for patients whose mental disorders were accompanied by drug and/or alcohol abuse to be less likely to be hospitalized than other patients.

### *Logistic Regression Analyses*

The first step in the logistic regression analysis was to compute a model including six variables that had been consistently shown in previous research to predict hospitalization: presence or absence of preadmission physical attacks and/or fear-inducing behavior, extent of suicidal behavior, primary diagnosis (schizophrenic or not, manic or not); and level of functioning as indicated by GAS score. To permit later cross-validation analyses, the model was derived on two-thirds of the sample (N=169), a subgroup that was randomly selected from the total sample after stratification by the variables to be included in the model. (The subsample of 169 patients is two-thirds of the 263 patients with complete data on all variables; 18% [N=58] of the 321 patients in the original sample had missing values on some variables and therefore could not be included in the regression analyses.) Two other variables, which have received some support in previous studies as predictors of hospitalization decisions (i.e., the presence of drug or alcohol problems in addition to mental disorders and the presence of physical attacks or fear-inducing behavior during the psychiatric emergency service visit) were then added to the model, which was subjected to a backward elimination procedure; neither of these additional variables

TABLE 1. Demographic Characteristics of Patients Who Were and Were Not Referred for Hospitalization From the Psychiatric Emergency Room

| | | | Disposition | | | |
|---|---|---|---|---|---|---|
| | Total (N=321) | | Hospitalized (N=124) | | Not Hospitalized (N=197) | |
| Variable | N | %[a] | N | %[a] | N | %[a] |
| Gender[b] | | | | | | |
| Male | 103 | 33.9 | 50 | 42.4 | 53 | 28. |
| Female | 201 | 66.1 | 68 | 57.6 | 133 | 71. |
| Unknown | 17 | | | | | |
| Age (years) | | | | | | |
| 18–29 | 85 | 26.8 | 28 | 23.0 | 57 | 29.3 |
| 30–39 | 124 | 39.1 | 49 | 40.2 | 75 | 38. |
| 40–49 | 53 | 16.7 | 17 | 13.9 | 36 | 18.5 |
| 50+ | 55 | 17.4 | 28 | 23.0 | 27 | 13.9 |
| Unknown | 4 | | | | | |
| Ethnicity | | | | | | |
| White | 176 | 55.4 | 65 | 52.4 | 111 | 57.2 |
| Nonwhite | 142 | 44.7 | 59 | 47.6 | 83 | 42.8 |
| Unknown | 3 | | | | | |
| Employed[c] | | | | | | |
| Yes | 33 | 11.0 | 6 | 5.3 | 27 | 14.4 |
| No | 268 | 89.0 | 108 | 94.7 | 160 | 85.6 |
| Unknown | 20 | | | | | |
| Residence | | | | | | |
| With family | 78 | 26.1 | 32 | 27.1 | 46 | 25.4 |
| Other | 221 | 73.9 | 86 | 72.9 | 135 | 74.6 |
| Unknown | 22 | | | | | |
| Referral source | | | | | | |
| Police | 108 | 33.9 | 44 | 35.5 | 64 | 32.3 |
| Other | 211 | 66.1 | 80 | 64.5 | 131 | 67.2 |
| Unknown | 2 | | | | | |

[a] Data are missing for some variables. Percents are based on total for the particular variable.

[b] $\chi^2$=5,60, df=1, $p<0.02$.

[c] $\chi^2$=5.20, df=1, $p<0.03$.

**TABLE 2. Clinical Characteristics of Patients Who Were and Were Not Referred for Hospitalization From the Psychiatric Emergency Room**

| | | | Disposition | | | |
|---|---|---|---|---|---|---|
| | Total (N=321) | | Hospitalized (N=124) | | Not Hospitalized (N=197) | |
| Variable | N | %[a] | N | %[a] | N | %[a] |
| Diagnosis[b] | | | | | | |
| Major depression | 18 | 5.6 | 12 | 9.7 | 6 | 3.1 |
| Manic episode | 31 | 9.7 | 16 | 12.9 | 15 | 7.7 |
| Organic brain syndrome | 18 | 5.6 | 8 | 6.5 | 10 | 5.3 |
| Schizophrenia | 101 | 31.7 | 64 | 51.6 | 37 | 19.0 |
| Other psychosis | 22 | 6.9 | 7 | 5.6 | 15 | 7.7 |
| Substance abuse | 69 | 21.6 | 5 | 4.0 | 64 | 32.8 |
| Other | 60 | 18.8 | 12 | 9.7 | 48 | 24.6 |
| Unknown | 2 | | | | | |
| GAS score[c] | | | | | | |
| 1–20 | 70 | 23.5 | 43 | 37.1 | 27 | 14.8 |
| 21–30 | 121 | 40.6 | 51 | 44.0 | 70 | 38.5 |
| 31–40 | 56 | 18.8 | 15 | 12.9 | 41 | 22.5 |
| 41+ | 51 | 17.1 | 7 | 6.0 | 44 | 24.2 |
| Unknown | 23 | | | | | |
| Preadmission suicidal behavior[d] | | | | | | |
| Present | 128 | 40.1 | 34 | 27.4 | 94 | 48.2 |
| Absent | 191 | 59.9 | 90 | 72.6 | 101 | 51.8 |
| Unknown | 2 | | | | | |
| Preadmission violence[e] | | | | | | |
| Physical attacks | 40 | 12.5 | 20 | 16.1 | 20 | 10.3 |
| Fear-inducing behavior | 59 | 18.5 | 28 | 22.6 | 31 | 15.9 |
| Absent | 220 | 69.0 | 76 | 61.3 | 144 | 73.9 |
| Unknown | 2 | | | | | |
| Violence in emergency room | | | | | | |
| Physical attacks | 14 | 4.4 | 8 | 6.5 | 6 | 3.1 |
| Fear-inducing behavior | 55 | 17.2 | 21 | 16.9 | 34 | 17.4 |
| Absent | 250 | 78.4 | 95 | 76.6 | 155 | 79.5 |
| Unknown | 2 | | | | | |
| Drug and/or alcohol problems in addition to mental problems[f] | | | | | | |
| Present | 74 | 23.2 | 22 | 17.7 | 52 | 26.7 |
| Absent | 245 | 76.8 | 102 | 82.3 | 143 | 73.3 |
| Unknown | 2 | | | | | |

[a] Data are missing for some variables. Percents are based on total for the particular variable.
[b] $\chi^2$=72.21, df=6, $p<0.0001$.
[c] $\chi^2$=32.53, df=3, $p<0.0001$.
[d] $\chi^2$=12.78, df=1, $p<0.0001$.
[e] $\chi^2$=5.65, df=2, $p<0.06$.
[f] $\chi^2$=2.91, df=1, $p<0.09$.

significantly ($p<0.05$) enhanced the predictive capacity of the model, so both were eliminated. Finally, several variables that some research has indicated are possibly useful in predicting hospitalization decisions (i.e., whether the subject resides with family, whether he or she is currently employed, referral source [police or other], age, gender, and interactions between manic or schizophrenic diagnosis and assaultive or fear-inducing behavior) were subjected to a forward selection procedure in which they were permitted to enter the model if this enhanced the predictive capacity of the model to a statistically significant degree ($p<0.05$). The only new variable to be retained after this step was gender.

Table 3 summarizes the final model resulting from the logistic regression analyses, which had an overall significance of $\chi^2$=45.48, df=7, $p<0.00001$. Clearly, violent and suicidal behaviors contributed little to the prediction of hospitalization decisions when diagnosis and overall severity of psychiatric impairment were taken into account. The clinical variables of diagnosis (schizophrenic or manic) and level of global impairment (GAS score) were the most important predictors of hospital admission. In addition to reporting the significance level of each variable in the model, table 3 gives odds ratios for each variable, i.e., the odds of hospitalization based on that variable when the other variables in the model are held constant. For dichotomous predictor variables (e.g., schizophrenic or not), the odds ratio represents the multiplicative change in the odds of hospitalization as the predictor changes from absence of a condition to presence of the condition; for continuous predictor variables (e.g., GAS score), the odds ratio represents the multiplicative change in the odds for each unit change in that predictor variable. The model correctly classified 73.4% of the patients, with a sensitivity of 78.3%, a specificity of 70.0%, a false-positive rate of 35.7%, and a false-negative rate of 17.6%.

To assess the stability of the prediction equation, we conducted a cross-validation analysis. We applied the previously mentioned model, which had been derived on two-thirds of the sample, to the remaining one-third of the sample. When the model was applied to the 94 subjects in the cross-validation subsample, 69.1% of the subjects were correctly classified, the sensitivity was 55.3%, the specificity was 78.6%, the false-negative rate was 27.9%, and the false-positive rate was 36.4%. Although some shrinkage in the sensitivity of the model would be expected on statistical grounds, the overall results of the cross-validation analysis suggest that the logistic regression models have a reasonable degree of stability in classifying which patients will and will not be hospitalized.

## DISCUSSION

These results suggest that clinical variables such as diagnosis and severity of psychiatric impairment are more important predictors of the decision to hospitalize patients from the psychiatric emergency room than are violent and suicidal behavior. In spite of legal pressures to focus on overt behaviors as a basis for liability prevention and civil commitment, clinicians in this study did not allocate inpatient resources to preventively detain persons unlikely to benefit from treatment. Rather, they hospitalized the most severely disturbed patients, with diagnoses such as schizophrenic and manic disorders for which a widely accepted therapeutic armamentarium exists. This finding is reassuring in that treatment objectives do not appear to have been neglected because of legal concerns about patient behavior. This result is also consistent with clinical recommendations that in the evaluation of the violent patient, attention needs to be given to the underlying disorder, since violent behavior itself can result from many diverse causes only some of which require inpatient treatment (5). Clearly, many patients who had displayed overt aggression before or after coming to the psychiatric emergency service were not felt to require inpatient psychiatric treatment and were instead referred to alternatives such as outpatient treatment, drug and alcohol programs, primary medical care, and the legal system.

Although our main research question was addressed by the multivariate analyses, examination of the individual patients' characteristics suggests similarities and differences between our sample and those of other studies on hospitalization decisions. As with other reports (9, 10), we found that diagnosis (e.g., of schizophrenia) and recent violence were associated with the decision to hospitalize. Our finding of an inverse relationship between recent suicidal behavior (e.g., threats and gestures) and hospitalization is unusual.

It is possible that an influence on these findings was the nature of our psychiatric emergency service, which has a holding area and staff on duty 24 hours per day. Gillig et al. (27) have reported that short-term holding areas in psychiatric emergency services can help avert hospitalization for many patients. Typical examples from our data set include patients with personality disorders or substance abuse disorders who came to the psychiatric emergency service during suicidal crises or who were intoxicated. In settings without access to a holding area, staff may have to hospitalize such patients.

**TABLE 3. Summary of Logistic Regression Analyses to Predict Odds of Hospitalization From the Psychiatric Emergency Room**

| Variable | Odds Ratio | Item $\chi^2$ | p |
|---|---|---|---|
| Schizophrenia diagnosis | 5.92 | 17.43 | <0.001 |
| GAS score | 0.94 | 8.95 | <0.003 |
| Manic episode diagnosis | 3.87 | 5.93 | <0.02 |
| Male gender | 2.28 | 4.40 | <0.04 |
| Suicidal behavior | 1.19 | 0.71 | n.s. |
| Preadmission physical attacks | 1.28 | 0.19 | n.s. |
| Preadmission fear-inducing behavior | 1.47 | 0.66 | n.s. |

This study focused on hospitalization decisions among a heterogeneous group of patients who were evaluated under a variety of legal and civil commitment circumstances. The results are consistent, however, with a study of emergency civil commitment by Segal et al. (28), who found that patients who were committed were more seriously ill and more dangerous.

Our finding that gender was associated with inpatient admission was puzzling, although some previous research has also reported this finding (10). Given reports that violence by psychiatric patients has a complex relationship with gender, depending on the setting (23), further study is needed to explain the association of patients' gender with clinical decision making about hospitalization.

We should point out that this report did not evaluate clinician variables such as the subjective explanation given by each clinician for his or her decisions. Although this is of interest, past research indicates that clinicians' explanations of their reasons typically are less predictive of the outcome for decisions than are empirical correlates of the decision (29) (such as those identified in this study). Future prospective studies are needed to assess how variables such as clinician training and the availability of specialized treatment resources (e.g., intensive case management, acute diversion units, and mobile crisis units) can affect the use of community-based treatment for patients whose clinical presentation includes violent behavior. The results of this study suggest a pattern of service delivery whereby the evaluation of individual patients considers the possibility of community-based treatment for patients depending on their mental disorder, even if the patients have displayed violent or suicidal behavior. Future research is needed to evaluate the impact of such decision-making patterns on patients' course and outcome.

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# Diagnosis of *DSM-III-R* Personality Disorders by Two Structured Interviews: Patterns of Comorbidity

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*Objective: The purpose of this study was to examine patterns of co-occurrence of axis II disorders in a group of consecutive patients evaluated with two contrasting structured interviews. Method: One hundred of 106 consecutive applicants for long-term, inpatient treatment of severe personality psychopathology were assessed, face-to-face, by psychiatrists using the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and the Personality Disorder Examination (PDE). The percent of co-occurrence of pairs of disorders diagnosed by each structured interview separately was calculated, and significance levels were determined by using chi-square tests of independence. Finally, odds ratios were computed for the odds of each pair of disorders occurring together compared with the odds for the occurrence of each disorder alone. Results: The two interview methods revealed different comorbidity patterns. Significant covariation was found for 29 pairs of disorders diagnosed with the PDE, compared with 12 pairs diagnosed with the SCID-II. Six pairs of disorders covaried significantly and were associated with odds ratios greater than 4: histrionic with borderline, histrionic with narcissistic, narcissistic with antisocial, narcissistic with passive-aggressive, avoidant with schizotypal, and avoidant with dependent. Conclusions: Substantial overlap occurred among personality disorders. In this group of patients, consistent patterns of comorbidity involving narcissistic, avoidant, and histrionic personality disorders suggest that categorical distinctions between them and certain other* DSM-III-R *personality disorders may be illusory. The question of which of two overlapping disorders is more valid, however, is left unanswered. For clinical purposes, a two-level diagnostic convention is proposed.*

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Comorbidity is an important but elusive concept in psychopathology. Diagnostic heterogeneity may contribute substantially to differences in research findings, leading to confusing, inconclusive, or contradictory results. Clinically, heterogeneity may contribute to differential treatment responses among superficially similar patients.

The capacity to differentiate syndromal complexity from multiple, discrete, coexisting disorders in a given patient may make a critical difference in a recommended treatment approach or a research design (1). For example, is *DSM-III-R* panic disorder with agoraphobia one disorder or two? If one, how is it that a syndrome of agoraphobia without a history of panic disorder (or even without limited symptom attacks) occurs? If two, how does the co-occurrence of these two presumably independent clinical states differ from the occurrence of intense anxiety that is considered an integral aspect of the syndrome of simple phobia? Is generalized social phobia a more severe form of the more limited type or is it a discrete disorder? With respect to axis II, it is unclear whether the 11 specific *DSM-III-R* diagnoses are different disorders, as demonstrated by the usual standards of diagnostic validity (e.g., discrete family histories or differential treatment responses) or if some, at least, are manifestations of more fundamental psychopathological disturbances (differing in severity, duration, stage of illness, aspect of functioning affected, or other nondiscrete variable).

The term "comorbidity" is generally used to mean coexisting disorders that have distinct etiologies, such as pneumonia and pneumothorax, or schizophrenia and toxic delirium. On axis II, disorders overlap extensively (2, 3), and most studies that have used semistructured interviews to systematically evaluate patients for all axis II disorders (3, 4) have found that at least 50% of patients have two or more coexisting personality dis-

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orders. It may be, then, that a dimensional approach is better suited for axis II disorders (5) than a categorical one that results in an unwieldy list of presumably comorbid diagnoses to describe "character pathology" in a given patient.

For example, borderline personality disorder has been shown to be transmitted in families (6), but it has also been shown to overlap extensively with other axis II disorders (7). Familial transmission has also been suggested for schizotypal (8), paranoid (9), and antisocial (10) personality disorders; the rest have not been studied from a family perspective. It is not clear if these disorders are transmitted independently of each other in families or if, instead, certain groups of axis II disorders coexist in patients and their families with regularity. To our knowledge, only one twin or adoption study of borderline personality disorder has been done to more specifically address its heritability (11). Biological markers have been proposed but not identified as specific for the disorder (12), and it has been suggested that borderline personality disorder may consist of several different disorders, including a subgroup representing an atypical affective disorder (13). Some researchers have posited that borderline personality disorder itself is a dimensional construct rather than a categorical one (7, 14, 15).

Widiger and Rogers (16) have argued that the three clusters of disorders on axis II (odd/eccentric, dramatic/emotional, and anxious/fearful) may be the more fundamental underlying conditions. Factor analytic studies have validated the cluster concept (17). On the basis of this model, the dramatic/emotional cluster could be a single personality disorder with different manifestations in behavior, similar to the notion of depression as a type of mood disorder with particular manifestations. Kernberg (18) has described a theoretical concept along these lines for borderline conditions, which he calls "borderline personality organization." His concept is of a general disturbance that includes not only the *DSM-III-R* category of borderline personality disorder but many of the other axis II disorders as well (19). Alternatively, such an underlying disorder could be an axis I disorder itself, such as depression, which, when chronic, leads to alterations in personality.

Most previously published studies on comorbidity among axis II disorders used either diagnoses made by clinical judgment rather than by research interviews (2, 7, 20) or *DSM-III* rather than *DSM-III-R* criteria (3, 20, 21). Until the emergence of semistructured, clinical research interviews, no systematic data were available to clarify the adequacy of a categorical approach to the diagnosis of personality psychopathology.

In the present report, we examine patterns of co-occurrence of axis II disorders in a group of 100 patients evaluated with two contrasting structured interviews, the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) (22) and the Personality Disorder Examination (PDE) (23). Differences in prevalence rates for any given disorder and presumed relationships between disorders may be due to differences in assessment methods (15, 24), sample selection (7), or changes in diagnostic criteria such as those which occurred for some axis II disorders when *DSM-III-R* replaced *DSM-III* (2). By using two different interviews based on *DSM-III-R* in the same patient group, our aim was to identify the similarities and differences between the interviews in results regarding diagnostic overlap. Consistent patterns of comorbidity, indicated by agreement between the two interviews that specific disorders were related, would suggest that categorical distinctions between certain *DSM-III-R* personality disorders may be illusory.

## METHOD

### *Subjects and Interviews*

One hundred of 106 consecutive applicants for long-term, inpatient treatment of severe personality psychopathology on our clinical research service were assessed, face-to-face, by psychiatrists using two semistructured interviews for diagnosing axis II personality disorders. Seventy-one percent of the subjects were women, 85% were white, 93% were at least high school graduates (38% were college graduates), 81% had never been married, and 66% had been employed during the year before the evaluation. The mean age of the subjects was 27.7 years (SD=6.2).

The two interviews, the SCID-II (22) and the PDE (23), were selected because they differ from each other in approach to the diagnosis of personality disorders and in scoring method, but each gives diagnoses based on *DSM-III-R* criteria. Each interview has been subjected to formal studies of reliability, and their reliabilities have been found to be comparable (25, 26).

*DSM-III-R* was in development during this study, and the criteria for personality disorders were being revised. At the time we initiated this study, both structured interviews contained the diagnostic criteria from the Oct. 5, 1985, draft of *DSM-III-R*. Before the data collection was complete, the criteria had undergone two revisions, in Aug. 1, 1986, and in the final draft manual, published on June 1, 1987. We revised our instruments once during the course of the study to correspond to the final axis II criteria. A comparison of the criteria in the Oct. 5, 1985, draft with the final manual's criteria reveals identical criteria content (but not necessarily wording) for schizotypal, histrionic, antisocial, obsessive-compulsive, and passive-aggressive personality disorders. Paranoid, narcissistic, borderline, and dependent personality disorders shared all but one criterion each in the two versions. Schizoid and avoidant personality disorders had two fewer criteria in the final *DSM-III-R* than in the preliminary draft. The category of personality disorders not otherwise specified was not used.

### *Assessment Procedure and Interviewers*

Eighty-eight of the 100 patients received both structured interviews on the same day. Of the remaining 12

**TABLE 1. Prevalence of Personality Disorders in 100 Patients Diagnosed With the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and the Personality Disorder Examination (PDE)**

| | Prevalence (%) | | Difference in Rates[b] | |
|---|---|---|---|---|
| Personality Disorder[a] | SCID-II | PDE | $\chi^2$ | p |
| Paranoid | 35 | 15 | 14.29 | <0.002 |
| Schizoid | 12 | 1 | 11.00 | <0.002 |
| Schizotypal | 18 | 19 | 0.06 | n.s. |
| Antisocial | 7 | 9 | 0.67 | n.s. |
| Borderline | 62 | 64 | 0.18 | n.s. |
| Histrionic | 25 | 17 | 4.57 | <0.10 |
| Narcissistic | 17 | 20 | 0.53 | n.s. |
| Avoidant | 50 | 40 | 4.55 | <0.10 |
| Dependent | 33 | 34 | 0.60 | n.s. |
| Obsessive-compulsive | 18 | 22 | 1.00 | n.s. |
| Passive-aggressive | 13 | 8 | 1.67 | n.s. |

[a] Applying the SCID-II resulted in 290 axis II diagnoses; applying the PDE resulted in 249 (paired t=2.50, df=99, p<0.02).
[b] McNemar's test, two-tailed (df=1).

**TABLE 2. Number of Axis II Personality Disorder Diagnoses in 100 Patients Diagnosed With the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and the Personality Disorder Examination (PDE)**

| Number of Personality Disorder Diagnoses | Number of Patients | |
|---|---|---|
| | SCID-II | PDE |
| None | 14 | 26 |
| 1 | 11 | 14 |
| 2 | 23 | 17 |
| 3 | 15 | 13 |
| 4 | 16 | 8 |
| 5 | 9 | 1[illegible] |
| 6 | 8 | [illegible] |
| 7 | 3 | [illegible] |
| 8 | 0 | 3 |
| 9 | 0 | 0 |
| 10 | 1 | 0 |
| 11 | 0 | 0 |

patients, three were reinterviewed within 1 week, six within 1 month, and three within 2 months. (Six patients in the original group of 106 consecutive patients who never received the second interview were excluded from the study.) The interviews and interviewers were alternated in order, resulting in a balanced design. Each interview was conducted blind to the result of the other.

Ninety percent of the diagnostic interviews were administered by three of us (A.E.S., H.D.K., and S.E.H.). All interviewers were trained directly by developers of the structured interviews.

### *Analyses*

The percent of co-occurrence of pairs of disorders diagnosed by each structured interview separately were calculated. The percent of co-occurrence was defined as the number of patients who had both of any pair of disorders divided by the number of patients who had either (15). Significance levels were determined by using chi-square tests of independence with Yates's correction for continuity on 2×2 contingency tables. Finally, odds ratios were computed for the odds of each pair of disorders occurring together compared with the odds for the occurrence of each disorder alone. In general, odds ratios greater than 2 were considered noteworthy, and doubling of the ratio (i.e., odds ratios of 4, 8, 16, etc.) was considered an increase in the order of magnitude of the association.

## RESULTS

Overall, in this study group of chronically and severely disabled patients, personality disorders were prevalent (table 1). The 100 patients were assigned 290 personality disorder diagnoses by the SCID-II and 249 by the PDE. The most prevalent axis II diagnosis on which the two interviews showed a general consensus was borderline personality disorder, followed by avoidant and dependent personality disorders. The SCID-II diagnosed more cases than the PDE of six disorders; two of these differences were statistically significant (paranoid and schizoid personality disorders), and two were different enough to indicate a trend (histrionic and avoidant). Agreement on specific diagnoses generated by the two interviews ranged from good for dependent (kappa=0.66), antisocial (kappa=0.59), and histrionic (kappa=0.58) personality disorders to poor for schizoid (kappa=0.14), passive-aggressive (kappa=0.21), and paranoid (kappa=0.29) personality disorders. Overall, agreement between the interviews was modest.

Although the absolute number of patients assigned diagnoses of axis II disorders was greater for the SCID-II than for the PDE (86 versus 74) ($\chi^2$=12.00, df=1, p<0.002, McNemar's test, two-tailed), the number of disorders per patient among patients who had any axis II disorders was the same—3.4 for each of the two methods. As shown in table 2, regardless of method, patients more often had more than one personality disorder than a single disorder. In no case did the PDE indicate that a patient had at least one personality disorder when the SCID-II did not as well.

Table 3 shows the percent of co-occurrence of the personality disorders diagnosed with the two methods. Significant covariation was found for 29 pairs of disorders diagnosed with the PDE, compared with only 12 pairs of disorders diagnosed with the SCID-II, even though the PDE yielded fewer total diagnoses of personality disorders than did the SCID-II (249 versus 290). Only one pair of disorders (schizoid with schizotypal) significantly co-occurred according to SCID-II assessments that did not also co-occur according to the PDE (the PDE diagnosed only one patient as schizoid in the entire group of 100), but 18 pairs were significant by the PDE but not by the SCID-II. Eleven pairs of disorders significantly co-occurred by both methods; they were paranoid with schizotypal, paranoid with borderline, paranoid with avoidant, schizotypal with avoid-

**TABLE 3. Co-Occurrence of Axis II Disorders in 100 Patients Diagnosed With the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and the Personality Disorder Examination (PDE)[a]**

| | Co-Occurrence of Each Personality Disorder[a] | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Personality Disorder | Paranoid | Schizoid | Schizotypal | Antisocial | Borderline | Histrionic | Narcissistic | Avoidant | Dependent | Obsessive-Compulsive | Passive-Aggressive |
| Paranoid | | | | | | | | | | | |
| SCID-II (N=35) | | 17.5 | 26.2$^{b}$ | 10.5 | 38.6$^{b}$ | 15.4 | 15.6 | 39.3$^{b}$ | 21.4 | 20.4 | 14.3 |
| PDE (N=15) | | 0.0 | 25.9$^{c}$ | 9.1 | 23.4$^{c}$ | 10.3 | 29.6$^{c}$ | 31.0$^{c}$ | 22.5$^{b}$ | 27.6$^{c}$ | 21.0$^{b}$ |
| Schizoid | | | | | | | | | | | |
| SCID-II (N=12) | | | 30.4$^{d}$ | 5.6 | 13.8 | 2.8 | 7.4 | 14.8 | 7.1 | 20.0 | 4.2 |
| PDE (N=1) | | | 0.0 | 0.0 | 1.5 | 0.0 | 0.0 | 2.5 | 0.0 | 0.0 | 0.0 |
| Schizotypal | | | | | | | | | | | |
| SCID-II (N=18) | | | | 4.2 | 19.4 | 10.3 | 12.9 | 30.8$^{d}$ | 18.6 | 20.0 | 3.3 |
| PDE (N=19) | | | | 12.0 | 25.8$^{b}$ | 9.1 | 34.5$^{d}$ | 40.5$^{d}$ | 32.5$^{d}$ | 28.1$^{c}$ | 8.0 |
| Antisocial | | | | | | | | | | | |
| SCID-II (N=7) | | | | | 11.3 | 14.3 | 20.0$^{b}$ | 5.6 | 2.6 | 8.7 | 17.6 |
| PDE (N=9) | | | | | 9.0 | 30.0$^{d}$ | 20.8$^{b}$ | 4.3 | 13.2 | 3.3 | 6.2 |
| Borderline | | | | | | | | | | | |
| SCID-II (N=62) | | | | | | 31.8$^{b}$ | 21.5 | 40.0 | 39.7$^{c}$ | 21.2 | 17.2 |
| PDE (N=64) | | | | | | 22.7$^{b}$ | 29.2$^{c}$ | 50.7$^{d}$ | 40.0$^{b}$ | 24.4$^{d}$ | 10.8 |
| Histrionic | | | | | | | | | | | |
| SCID-II (N=25) | | | | | | | 35.5$^{d}$ | 13.6 | 23.9 | 4.9 | 18.8 |
| PDE (N=17) | | | | | | | 27.6$^{c}$ | 11.8 | 24.4$^{b}$ | 14.7 | 13.6 |
| Narcissistic | | | | | | | | | | | |
| SCID-II (N=17) | | | | | | | | 13.6 | 16.3 | 12.9 | 25.0$^{c}$ |
| PDE (N=20) | | | | | | | | 27.7$^{b}$ | 50.0$^{d}$ | 27.3$^{b}$ | 21.7$^{c}$ |
| Avoidant | | | | | | | | | | | |
| SCID-II (N=50) | | | | | | | | | 43.1$^{d}$ | 23.6 | 12.5 |
| PDE (N=40) | | | | | | | | | 45.1$^{d}$ | 29.2$^{b}$ | 11.6 |
| Dependent | | | | | | | | | | | |
| SCID-II (N=33) | | | | | | | | | | 34.4$^{b}$ | 15.0 |
| PDE (N=34) | | | | | | | | | | 27.3$^{b}$ | 16.7$^{b}$ |
| Obsessive-compulsive | | | | | | | | | | | |
| SCID-II (N=18) | | | | | | | | | | | 19.2 |
| PDE (N=22) | | | | | | | | | | | 11.1 |
| Passive-aggressive | | | | | | | | | | | |
| SCID-II (N=13) | | | | | | | | | | | |
| PDE (N=8) | | | | | | | | | | | |

[a] Co-occurrence was calculated from 2×2 tables and defined as the number of patients with both disorders divided by the number with either. Significance levels were determined by chi-square tests of independence with Yates's correction for continuity on 2×2 contingency tables.
[b] $p<0.05$.
[c] $p<0.01$.
[d] $p<0.001$.

ant, antisocial with narcissistic, borderline with histrionic, borderline with dependent, histrionic with narcissistic, passive-aggressive with narcissistic, avoidant with dependent, and obsessive-compulsive with dependent. The most significant covariations observed by both methods were for avoidant with schizotypal personality disorder and avoidant with dependent personality disorder.

Table 4 presents the odds ratios for the pairs of disorders as diagnosed by both interviews. Odds ratios are less sensitive than co-occurrence percentages to differences in marginal probabilities and, thus, to disparate base rates or prevalences. Odds ratios may be the preferred measure of comorbidity because they allow comparisons to be made across different study groups (27). Diagnoses made by the PDE were associated with many more notable odds ratios than diagnoses by the SCID-II; e.g., use of the PDE resulted in at least twice as many odds ratios greater than 4 and 8 and the only odds ratios greater than 16 and 32. With the effect of prevalence reduced, seven pairs of disorders were associated with high (greater than 4) odds ratios by both methods: histrionic with antisocial, histrionic with borderline, histrionic with narcissistic, narcissistic with antisocial, narcissistic with passive-aggressive, avoidant with schizotypal, and avoidant with dependent.

## DISCUSSION

By employing two axis II interviews and examining their consensus, we have attempted to identify consistent patterns of comorbidity among personality disorders. Were there axis II disorders that invariably co-occurred with either method?

The SCID-II diagnosed a greater number of disorders overall than did the PDE, but the SCID-II demonstrated considerably fewer patterns of significant co-occurrence. As we have discussed elsewhere (28), the formats of the SCID-II and the PDE are markedly different, and the possibility of a "halo effect" is more likely to occur with the SCID-II. A halo effect might be expected to

**TABLE 4. Odds Ratios for Co-Occurrence of Axis II Disorders in 100 Patients Diagnosed With the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) and the Personality Disorder Examination (PDE)**

| | Odds Ratio for Each Personality Disorder | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Personality Disorder | Paranoid | Schizoid | Schizotypal | Antisocial | Borderline | Histrionic | Narcissistic | Avoidant | Dependent | Obsessive-Compulsive | Passive-Aggressive |
| Paranoid | | | | | | | | | | | |
| SCID-II (N=35) | | 3.0 | 3.8 | 2.7 | 2.9 | 0.8 | 1.4 | 3.3 | 1.1 | 2.2 | 1.7 |
| PDE (N=15) | | 1.8 | 5.3 | 1.7 | 22.9 | 1.3 | 7.0 | 14.0 | 3.6 | 5.8 | 7.4 |
| Schizoid | | | | | | | | | | | |
| SCID-II (N=12) | | | 9.8 | 1.2 | 2.0 | 0.2 | 1.0 | 2.2 | 0.6 | 4.1 | 0.6 |
| PDE (N=1) | | | 1.4 | 3.2 | 1.7 | 1.6 | 1.3 | 4.6 | 0.6 | 1.1 | 3.6 |
| Schizotypal | | | | | | | | | | | |
| SCID-II (N=18) | | | | 0.7 | 1.8 | 0.8 | 1.5 | 11.3 | 1.8 | 2.9 | 0.3 |
| PDE (N=19) | | | | 2.3 | 6.1 | 0.9 | 7.9 | 21.4 | 6.2 | 4.7 | 1.5 |
| Antisocial | | | | | | | | | | | |
| SCID-II (N=7) | | | | | 10.4 | 4.6 | 8.2 | 0.7 | 0.3 | 1.9 | 6.2 |
| PDE (N=9) | | | | | 1.1 | 14.5 | 6.3 | 0.4 | 2.7 | 0.4 | 1.5 |
| Borderline | | | | | | | | | | | |
| SCID-II (N=62) | | | | | | 4.4 | 3.4 | 1.2 | 4.1 | 2.5 | 3.9 |
| PDE (N=64) | | | | | | 5.2 | 14.8 | 7.5 | 3.9 | 38.6 | 4.3 |
| Histrionic | | | | | | | | | | | |
| SCID-II (N=25) | | | | | | | 9.0 | 0.5 | 2.0 | 0.3 | 3.1 |
| PDE (N=17) | | | | | | | 5.3 | 0.8 | 3.5 | 1.6 | 3.3 |
| Narcissistic | | | | | | | | | | | |
| SCID-II (N=17) | | | | | | | | 0.9 | 1.5 | 1.5 | 5.9 |
| PDE (N=20) | | | | | | | | 3.6 | 36.0 | 4.2 | 8.6 |
| Avoidant | | | | | | | | | | | |
| SCID-II (N=50) | | | | | | | | | 5.3 | 3.2 | 1.2 |
| PDE (N=40) | | | | | | | | | 6.0 | 3.5 | 2.7 |
| Dependent | | | | | | | | | | | |
| SCID-II (N=33) | | | | | | | | | | 3.2 | 1.9 |
| PDE (N=34) | | | | | | | | | | 3.1 | 6.9 |
| Obsessive-compulsive | | | | | | | | | | | |
| SCID-II (N=18) | | | | | | | | | | | 3.6 |
| PDE (N=22) | | | | | | | | | | | 2.3 |
| Passive-aggressive | | | | | | | | | | | |
| SCID-II (N=13) | | | | | | | | | | | |
| PDE (N=8) | | | | | | | | | | | |

lead to more frequent diagnoses in some categories because the interviewer can probe for confirmation of an emerging positive diagnosis as a particular category is being surveyed. On the other hand, the halo effect may also lead to less frequent diagnoses if they are prematurely dismissed after a different positive diagnosis seems likely. In addition, as discussed elsewhere (28), the algorithms for the PDE that establish thresholds for the presence or absence of criteria are more stringent than the guidelines of the SCID-II, and, as a result, fewer diagnoses in most categories are made.

Higher base rates of disorders are generally associated with higher rates of co-occurrence, but high co-occurrence rates or the percent of co-occurrence may not reflect comorbidity. Widiger et al. (15) evaluated available studies of personality disorders that included sufficient data to analyze co-occurrence percentages for all *DSM-III* axis II disorders (2, 3, 20, 21). They pointed out that percentages may be misleading if considered incorrectly. For example, when evaluating all patients who have one or the other or both of a pair of personality disorders, half of the patients with each disorder will also have the other disorder when the co-occurrence rate is only 33%.

Eleven pairs of disorders diagnosed with both the PDE and the SCID-II significantly ($p<0.05$ or greater) covaried. When both interviews demonstrate significant patterns of co-occurrence, the likelihood that these patterns are meaningful and nonrandom is greater. Comorbidity analysis, however, should take into account widely disparate base rates. We used odds ratios to reduce the effect of difference in base rates. Six of the seven pairs of disorders with odds ratios of 4 or greater by both the PDE and SCID-II were also significant ($p<0.05$ or greater) according to co-occurrence percentages. The one exception was the co-occurrence of antisocial with histrionic personality disorder, which was significant by the PDE ($p<0.001$) but not by the SCID-II.

In this group of patients, therefore, the most significant comorbidity, as measured by two interviews and analyzed by two methods, occurred in six pairs of disorders. Three of these involved narcissistic personality disorder (with antisocial, histrionic, and passive-aggressive personality disorders). Two involved avoidant personality disorder (with schizotypal and dependent personality disorders). The sixth pair was borderline with histrionic personality disorder.

The analysis of Widiger et al. (15) also led them to conclude that comorbidity appears to be the norm in personality disorders. In their review, the diagnosis most frequently co-occurring with other axis II diagnoses was borderline personality disorder. However, three of the four studies they reviewed (3, 20, 21) were based on *DSM-III* data, and in the fourth study, Morey (2) pointed out that the revisions made by *DSM-III-R* substantially increased the degree of diagnostic overlap between the different axis II disorders. Although the prevalence of borderline personality disorder diagnoses remained about the same, the prevalence of some personality disorder diagnoses increased markedly with *DSM-III-R* criteria: e.g., 240% for avoidant, 300% for paranoid, 350% for narcissistic, and 800% for schizoid personality disorder. The two pairs of *DSM-III-R* disorders in Morey's study that had the highest percent of overlap were schizotypal with avoidant and schizotypal with paranoid personality disorder. Our results replicate the former relationship but not the latter.

A number of investigators (3, 20, 21, 29) have found high rates of co-occurrence of borderline and histrionic personality disorders defined by *DSM-III* criteria. In drafting *DSM-III-R,* specific efforts were made to reduce the degree of overlap between these disorders, yet in our data there remains significant co-occurrence of borderline and histrionic personality disorders defined by *DSM-III-R* criteria. We did not find significant overlap between borderline and narcissistic disorders, in contrast to the results of Pfohl et al. (3). We found only a questionable (by the PDE only) relationship of borderline personality disorder to schizotypal personality disorder. This is surprising, given the degree to which comorbidity research on borderline personality disorder has focused on this association (30, 31).

Trull et al. (32) studied *DSM-III* avoidant, schizoid, and dependent personality disorders and found that 71% of their avoidant patients were also dependent and that 50% of the dependent patients were also avoidant; these data are compatible with our findings. Avoidant personality disorder has been shown by others to overlap significantly with schizotypal personality disorder (3, 33), which is consistent with our data, and with paranoid personality disorder (21), which corresponds to our results based on co-occurrence percentages but not when adjusted for base rates by using odds ratios. Trull et al. did not find co-occurrence of schizoid and either dependent or avoidant personality disorders—also compatible with our data.

## RESEARCH AND CLINICAL IMPLICATIONS

As already mentioned, controversy persists regarding whether patterns of comorbidity on axis II represent independent disorders co-occurring in the same patients or, as Widiger and Frances (5) have argued, indicate that a dimensional system is more appropriate than the categorical system currently applied. Overlap in the content of diagnostic criteria for different disorders continues in *DSM-III-R,* and some of the disorders that co-occurred significantly with both diagnostic methods in this study have content overlap in their criteria. For example, narcissistic personality disorder co-occurred with histrionic, passive-aggressive, and antisocial personality disorders. Not only are these associations clinically intuitive, but selected criteria are either identical or similar for these disorders. A similar point can be made about the other three pairings that were significant with both interview methods by both co-occurrence rates and odds ratios, namely, schizotypal with avoidant, dependent with avoidant, and histrionic with borderline personality disorder. As an illustration of this overlap, "constantly seeks or demands reassurance or praise" is a criterion for histrionic personality disorder and "requires constant attention and admiration" is a criterion for narcissistic personality disorder. Similarly, "has no close friends or confidants" is a criterion for both schizotypal and avoidant personality disorders.

Certain co-occurrences in the PDE data seem clinically counterintuitive. For example, narcissistic and dependent or borderline and obsessive-compulsive personality disorders do not seem likely partners. Although theoretical constructs could be suggested (e.g., that a fear of dependency or engulfment produces the grandiose pseudo-independence of narcissism or that the chaotic impulsiveness of borderline personality disorder is defensively counteracted by attempts at rigid orderliness), it seems unlikely that questions based on *DSM-III-R* criteria, themselves aimed at measurable or observable behavior, would elicit such responses, even if they were present. It may be that the format of the 1985 PDE makes it more difficult for the clinician to weigh the meaning and importance of answers to individual questions because they are not keyed to specific disorders in the body of the interview itself. Thus, the clinician would not have the advantage of probing or challenging inconsistent or contradictory responses as he or she would with the SCID-II. This problem has been corrected to some extent in the 1988 version of the PDE (25).

Although the SCID-II pattern of comorbidity may seem to have more face validity, the halo effect mentioned earlier may have led to discovery of the expected. Interviewers may have operated on their clinical intuitions concerning which disorders they believed to be associated and which not and consciously or unconsciously may have altered their diagnostic thresholds accordingly. Widiger and Frances (34) have argued that an interview with a format similar to that of the PDE, which discourages diagnostic biases, is preferable in research on overlap between diagnostic criteria sets. Our use in this study of both interviews and our focus on congruent results would appear to balance the positive and negative aspects of either interview used alone.

In this group of patients with long-term and extensive psychopathology, certain apparent disorders might be derivatives or secondary by-products of pervasive axis I illness rather than coexisting independent conditions. Many of these patients, although referred for treatment of axis II pathology, had concomitant mood and anxiety disorders on axis I (our data in preparation). These axis I disorders may show consistent patterns of covariation with certain axis II disorders. Avoidant personality disorder, for example, could then be an "epiphenomenon," reflecting generally high anxiety levels or a behavioral pattern secondary to many years of illness.

Narcissistic personality disorder has been a controversial addition to the diagnostic nomenclature (35). We found here that it covaried with antisocial, histrionic, and passive-aggressive personality disorders, possibly implying certain underlying common features such as self-interest or insensitivity to others. From a clinical perspective, the disorders represent different psychopathological constructs, but whether narcissistic personality disorder is valid as a disorder in its own right or is a feature of other disorders is not clear.

Demonstration of significant and conceptually coherent overlap between diagnoses leaves unanswered the question of which of two overlapping disorders is the more valid. As yet, there is no clear-cut way to resolve this issue with respect to the personality disorders. Arguments may be made on the basis of theoretical models or historical tradition that one of the two overlapping disorders should be considered predominant and subsume the other, but counterarguments are also possible. The real question is whether each of the two diagnosed disorders contributes independently to some important clinical variable. Research designed to determine the unique contribution of individual personality disorder diagnoses to variation in external validators of personality psychopathology is sorely needed.

Our data suggest that there may be merit in maintaining the categorical diagnostic system to allow further research to be done. The two interviews used in this study did not produce identical prevalence rates or patterns of significant co-occurrence. Some specific disorders, such as antisocial personality disorder, may be readily assessed cross-sectionally; others may need longitudinal clinical observation for accurate assessment (36). Given the rates of multiple diagnoses and percents of co-occurrence found, however, we believe that a persuasive case can be made for a two-level diagnostic system on axis II for clinical use. For patients who meet criteria for two or fewer disorders (focal personality disorder), the current categorical system might be retained. For patients with more than two disorders, a single diagnosis of "extensive personality disorder" might be made, with a dimensional description of the predominant characteristics of the disorder. For example, a patient meeting criteria for three axis II disorders might be diagnosed as having "extensive personality disorder with paranoid, borderline, and narcissistic features." Such a method would allow continuity with research methodology incorporating the current axis II approach but would create a diagnostic convention that corresponds better with clinical practice. This hierarchy would require empirical testing and comparison with previously proposed hierarchies for personality disorders based on severity, such as those of Kernberg (18) and Millon (37).

A limitation of this study is its focus on severely ill patients whose personality psychopathology resulted in more than one personality disorder diagnosed with structured assessment methods. The findings may not generalize to outpatients who are less ill. We have recently completed a replication in a more highly functioning group of outpatients applying for psychoanalysis and are in the process of analyzing these data.

Future efforts should also attempt to further reduce overlap among the personality disorders by eliminating duplicate criteria and by identifying or developing criteria that can discriminate one diagnosis from another. Finally, it may eventually prove fruitful to collapse current categories into supraordinate groupings on the basis of factor analysis, multidimensional scaling, or other statistically based hierarchies.

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# Self-Mutilation in Personality Disorders: Psychological and Biological Correlates

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*Objective: The goal of this study was to determine whether self-mutilators with personality disorders differ from nonmutilators with personality disorders in impulsivity, aggression, and other psychopathology and whether serotonergic dysfunction contributes to self-mutilation. Method: Twenty-six self-mutilators with personality disorders were matched to 26 control subjects with personality disorders for gender, age, education, axis I diagnosis of affective disorder, and axis II diagnosis of personality disorder. Numerous indexes of psychopathology as well as CSF 5-hydroxyindoleacetic acid (5-HIAA) levels and platelet imipramine binding sites ($B_{max}$) and affinity ($K_d$) were determined. Results: Self-mutilators had significantly more severe character pathology, had greater lifetime aggression, and were more antisocial than the control subjects. The self-mutilators scored higher on the Hamilton Rating Scale for Depression but not on the Beck Depression Inventory or the Beck Hopelessness Scale. The two groups did not differ on the Buss-Durkee Hostility and Guilt Inventory or on the Sensation Seeking Scale. The degree of self-mutilation was significantly correlated with impulsivity, chronic anger, and somatic anxiety. Both self-mutilation and impulsivity showed significant negative correlations with $B_{max}$, although the two groups did not differ in CSF 5-HIAA levels or in platelet imipramine binding. Conclusions: The results demonstrate the contribution of severe character pathology, aggression, impulsivity, anxiety, and anger to self-mutilation and provide preliminary support for the hypothesis of underlying serotonergic dysfunction facilitating self-mutilation.*

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Self-mutilation is defined as deliberate harm to one's own body resulting in tissue damage, without a conscious intent to die. It is encountered predominantly in three groups of patients: in those with mental retardation and other organic conditions (stereotypic self-mutilation such as head banging), in those with psychoses (major self-mutilation such as self-enucleation and autocastration), and in those with personality disorders—commonly borderline personality disorder and, in incarcerated men, antisocial personality disorder (minor self-mutilation such as cutting or burning the skin) (1).

The phenomenon of self-mutilation has received relatively little attention in the psychiatric literature. The clinical literature on self-mutilation in patients with personality disorders consists mostly of descriptive, uncontrolled, and retrospective studies that present a bewildering and complex array of etiologies and psychopathological correlates without sufficient systematic observation and comparison. Typically, the behavior begins in adolescence and may persist for decades and result in great personal and social morbidity. The term "deliberate self-harm" has been proposed to delineate this behavior as a distinct syndrome of low lethality and repetitive, direct self-destructive behavior (2).

Relief of mounting tension and depersonalization is the single most common clinically identified correlate to self-mutilation; other cited psychological motivations include venting of anger, establishing control, forming an identity, influencing others, responding to self-hatred or guilt, discharging sexual feelings, and seeking euphoria. Underlying psychodynamic hypotheses are equally varied and include partial suicide as an attempt at self-healing, rage toward the self or the internalized bad object, symbolic castration, formation of ego boundaries, autoerotic gratification, mastery of menstruation, and procurement of a transitional object (1).

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Social and cultural perspectives may also enrich our understanding of self-mutilating behavior (3); review of these perspectives is beyond the scope of this paper.

There are very few systematic studies, most of which involved a small number of subjects, and even fewer controlled studies investigating self-mutilation in personality disorders. Rosenthal et al. (4) compared female inpatients who had histories of wrist-cutting with female inpatients who had histories of suicide attempts by methods other than wrist-cutting. The women who cut themselves were more likely to have histories of early trauma and surgery, difficulties with menses, sexual identity confusion, chronic feelings of emptiness, and histories of eating disorders; the comparisons were not tested statistically and the diagnoses of the patients in the two groups were not specified. Schaffer et al. (5) compared self-mutilators with demographically matched subjects who had psychiatric disorders and found that the self-mutilators were much more likely to have borderline personality disorder. McKerracher et al. (6) and Gardner and Gardner (7) compared self-mutilators with nonmutilators who did not differ in their diagnoses of personality disorders and found that self-mutilators were significantly more obsessional. Bennum (8) compared self-mutilators with nonmutilating depressed patients and found that the two groups did not differ in depression or inwardly directed hostility but that the self-mutilators had greater outwardly directed hostility. Roy (9) compared self-mutilators, most of whom were diagnosed as having personality disorders, with control subjects, most of whom were diagnosed as having depressive neurosis, and found greater introversion, neuroticism, and hostility in the self-mutilators. These controlled studies provide a useful beginning to the systematic study of the psychology of self-mutilation, but the conclusions we can draw on the basis of their findings are limited by the heterogeneity of the groups compared and the diversity of the psychological variables investigated and the assessment instruments used.

Biological studies of self-mutilation in patients with personality disorders have been very limited. Coid et al. (10) conducted one study of the opiatergic system in habitual self-mutilators and found them to have higher plasma metenkephalin than control subjects. The potential role of the serotonergic system in self-mutilation is of great theoretical interest. Serotonergic dysfunction has been widely implicated in suicide, an act of aggression toward oneself, across diagnostic groups (11), as well as in acts of impulsiveness and aggression toward others. There have been several studies of the serotonergic system specifically in personality disorders, focusing on aggressive and impulsive behaviors. These studies have shown a relationship between low CSF 5-hydroxyindoleacetic acid (5-HIAA) levels and suicide attempts (12), history of aggressive behavior (12), impulsive nonviolence such as arson (13), and impulsive violent offenses (14). Similarly, Coccaro et al. (15) showed a correlation between blunted prolactin response to the 5-hydroxytryptamine (5-HT) agonist fenfluramine, indicating reduced central net serotonin transmission, and a history of suicide attempts, aggression, assault, irritability, and motor impulsiveness in subjects with personality disorders. Stoff et al. (16) and Birmaher et al. (17) studied children with conduct disorders and found a significant negative correlation between impulsive and aggressive behaviors and platelet imipramine binding, a peripheral marker thought to represent central presynaptic serotonin release.

In one study of serotonergic function in personality disorders that examined self-mutilation, Gardner et al. (18) compared 17 women who had borderline personality disorder with 17 normal control subjects and found no difference in CSF 5-HIAA levels between the two groups, as well as no difference in CSF 5-HIAA levels between the 12 self-mutilators and the five nonmutilators in the borderline group. The different rates of suicide attempters in these two subgroups (58% and 100%, respectively), however, may have confounded the results. The aggression and impulsivity characteristics of self-mutilation suggest the possibility that this behavior may indeed be mediated in part by an underlying serotonergic dysfunction. The potential role of other neurotransmitter systems such as the opiatergic and the dopaminergic (19) are beyond the scope of this investigation. This is the first study aimed at determining whether self-mutilators with personality disorders differ from nonmutilators with personality disorders in measures of serotonergic function and whether these measures correlate with self-mutilating behavior, aggression, impulsivity, and other associated psychopathology.

## METHOD

Twenty-six self-mutilators with personality disorders and 26 control subjects with personality disorders were drawn from a larger pool of 202 suicide attempters and diagnostic control subjects studied by Stanley et al. (work in progress). Out of a total of 43 self-mutilators in the larger study group, 11 were excluded because they had an axis I diagnosis of psychotic disorder and six were excluded because they had an axis I diagnosis of affective disorder without an axis II disorder. The remaining 26 self-mutilators had axis II diagnoses and are the subjects of this study. All patients and control subjects consented to participation in the study after its nature had been explained to them.

Self-mutilation was defined as deliberate injury to one's own body tissue without conscious intent to die. Self-mutilation was assessed by clinical interview with the Schedule for Interviewing Borderlines (20), which rates the degree of self-mutilation on a frequency scale of 1 to 4 on which 1=none, 2=mild (1–3 times per year), 3=moderate (4–11 times per year), and 4=severe (more than 12 times per year). The mean self-mutilation score in the self-mutilator group was 2.7 (SD=0.8). Half (N=13) of the 26 patients had a self-mutilation score of 2, 35% (N=9) had a score of 3, and 15% (N=4) had a score of 4. The 26 self-mutilators with personality disorders were matched to 26 control subjects out of the pool of 159 nonmutilators to maximize similarity in gender (20 women and six men), age, education, axis I diagnosis of affective disorder, and axis II diagnosis of personality disorder (table 1). The mean age of the self-mutilators was 31.0 years (SD=9.6); that of the nonmutilators was 31.4 (SD=9.4) (t<1, df=50, n.s.).

*DSM-III-R* diagnoses were determined by clinical interviews in combination with the Schedule for Affective Disorders and Schizophrenia (21) and the Schedule for Interviewing Borderlines (20). The two groups did not differ in their suicide attempt histories (table 1). Suicide attempts were defined as acts committed with a conscious intent to end one's life and requiring medical attention; by definition, suicide attempts and acts of self-mutilation are mutually exclusive.

Patients were hospitalized throughout the study. All patients underwent a medical examination and standard laboratory tests to ensure their ability to participate. Inclusion criteria were age 18 to 85 years. Exclusion criteria were physical conditions precluding a lumbar puncture, neurological disorders, history of head trauma, brain damage, mental retardation or other substantial cognitive impairment, and a current diagnosis of substance use, which could potentially confound neurochemical assessments. Patients who were receiving medication affecting the CNS entered a medication-free phase for 14 days or longer, after which the lumbar puncture was performed. Venipuncture immediately followed the lumbar puncture, and full clinical evaluations were completed within 72 hours.

Several measures designed to assess specific areas of psychopathology were administered. To assess depression, three scales were used: 1) the Hamilton Rating Scale for Depression, 2) the Beck Depression Inventory, and 3) the Beck Hopelessness Scale (22). To assess personality, five scales were used: 1) the Schedule for Interviewing Borderlines, Part II: Schedule for Borderline Personalities (20), a semistructured interview with 11 subscales that assess a broad range of borderline traits, 2) a semistructured interview of each patient's lifetime history of aggression that provides quantifiable information on multiple aspects of aggressive behavior such as tantrums, fights, arguments, assaults and illegal acts, 3) the MMPI psychopathic deviance subscale, a self-rating that assesses antisocial traits, 4) the Buss-Durkee Hostility and Guilt Inventory (23), a self-rating of seven subscales of hostility (assault, irritability, resentment, indirect hostility, negativism, suspiciousness, and verbal hostility) as well as guilt, and 5) the Sensation Seeking Scale (24), self-rated on four subscales (thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility).

Biological measures included 1) CSF 5-HIAA levels, determined by high performance liquid chromatography using electrochemical detection, according to a method described elsewhere (25), and 2) number of platelet imipramine binding receptor sites ($B_{max}$) and affinity constant ($K_d$), determined by a method described elsewhere (26).

**TABLE 1. Characteristics of Subjects With Personality Disorders Who Were or Were Not Self-Mutilators**

| | Self-Mutilators (N=26) | | Nonmutilators (N=26) | | Comparison | | |
|---|---|---|---|---|---|---|---|
| Item | N | % | N | % | $\chi^2$ | df | |
| Education | | | | | <1 | 1 | n.s. |
| Not college graduate | 12 | 46.2 | 14 | 53.8 | | | |
| College graduate | 14 | 53.8 | 12 | 46.2 | | | |
| Axis I diagnosis | | | | | 3.00 | 4 | n.s. |
| None | 2 | 7.7 | 4 | 15.4 | | | |
| Dysthymia | 7 | 26.9 | 5 | 19.2 | | | |
| Major depression | 16 | 61.5 | 16 | 61.5 | | | |
| Bipolar, depressed | 1 | 3.8 | 0 | 0.0 | | | |
| Bipolar, mixed | 0 | 0.0 | 1 | 3.8 | | | |
| Axis II diagnosis | | | | | 3.03 | 7 | n.s. |
| Borderline | 15 | 57.7 | 16 | 61.5 | | | |
| Mixed | 6 | 23.1 | 6 | 23.1 | | | |
| Dependent | 1 | 3.8 | 1 | 3.8 | | | |
| Avoidant | 0 | 0.0 | 1 | 3.8 | | | |
| Histrionic | 1 | 3.8 | 0 | 0.0 | | | |
| Obsessive-compulsive | 1 | 3.8 | 1 | 3.8 | | | |
| Schizoid | 1 | 3.8 | 0 | 0.0 | | | |
| Schizotypal | 1 | 3.8 | 1 | 3.8 | | | |
| History of suicide attempts[a] | 21 | 80.8 | 19 | 73.1 | <1 | 1 | n.s. |

[a] The self-mutilators had made a mean of 3.0 (SD=3.1) suicide attempts; the nonmutilators had made a mean of 2.2 (SD=2.5) (t=1.10, df=47, n.s.).

For data analysis, two-group t tests were used to compare self-mutilators with control subjects on all continuous demographic, psychopathological, and biological measures. Chi-square tests were used to compare educational level, axis I diagnoses, axis II diagnoses, and rate of suicide attempts in the two groups. Pearson correlations were computed between self-mutilation and psychopathological variables and biological measures. All probability values are two-tailed. Because this study was exploratory in nature, multiple zero order correlations and t tests were performed, not accounting for the overall number of analyses. This process is designed to generate further areas of investigation.

## RESULTS

### *Measures of Psychopathology*

The total mean Hamilton depression scale score of the self-mutilators was significantly higher than that of the control subjects (table 2). This difference was accounted for by greater anxiety and somatization and greater cognitive disturbance rather than by vegetative factors. The two groups did not differ in their scores on the Beck Depression Inventory and the Beck Hopelessness Scale (table 2).

**TABLE 2. Scores on Measures of Psychopathology of Subjects With Personality Disorders Who Were or Were Not Self-Mutilators**

| | Self-Mutilators[a] | | Nonmutilators[a] | | Comparison[b] | |
|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | t | p |
| Hamilton Rating Scale for Depression | | | | | | |
| Total | 24.8 | 5.1 | 19.8 | 10.2 | 2.25 | ≤0.05 |
| Anxiety and somatization | 1.0 | 0.4 | 0.7 | 0.4 | 2.84 | ≤0.01 |
| Weight loss | 0.5 | 0.8 | 0.6 | 0.9 | <1 | n.s. |
| Cognitive disturbance | 1.2 | 0.5 | 0.9 | 0.6 | 2.15 | ≤0.05 |
| Diurnal variation | 0.6 | 0.7 | 0.5 | 0.7 | <1 | n.s. |
| Retardation | 1.7 | 0.7 | 1.6 | 0.8 | <1 | n.s. |
| Sleep disturbance | 1.1 | 0.7 | 0.8 | 0.6 | 1.69 | n.s. |
| Beck Depression Inventory | 30.1 | 11.9 | 27.6 | 15.2 | <1 | n.s. |
| Beck Hopelessness Scale | 10.8 | 4.9 | 8.9 | 6.0 | 1.18 | n.s. |
| Schedule for Interviewing Borderlines | | | | | | |
| Impulsivity | 14.1 | 4.4 | 13.1 | 4.3 | <1 | n.s. |
| All physically self-damaging acts | 8.6 | 1.9 | 6.2 | 1.8 | 4.68 | ≤0.001 |
| Unstable relationships | 7.7 | 2.8 | 6.1 | 2.2 | 2.28 | ≤0.05 |
| Compulsive sociability | 1.9 | 0.9 | 1.4 | 0.7 | 2.25 | ≤0.05 |
| Affective instability | 2.4 | 1.0 | 1.8 | 1.1 | 1.93 | ≤0.10 |
| Inappropriate chronic anger | 2.4 | 0.9 | 1.9 | 0.9 | 1.83 | ≤0.10 |
| Chronic emptiness | 3.0 | 0.9 | 2.1 | 1.0 | 3.40 | ≤0.001 |
| Chronic anxiety | 4.7 | 1.3 | 3.6 | 1.3 | 2.84 | ≤0.01 |
| Mood elevation after praise | 1.2 | 0.9 | 1.5 | 0.7 | <1 | n.s. |
| Rejection sensitivity | 3.2 | 0.8 | 2.7 | 0.9 | 2.21 | ≤0.05 |
| Identity disturbance | 9.4 | 2.8 | 7.4 | 2.3 | 2.72 | ≤0.01 |
| History of aggression | 21.0 | 4.7 | 16.1 | 4.7 | 3.70 | ≤0.001 |
| MMPI psychopathic deviance | 28.8 | 4.2 | 24.5 | 4.1 | 3.68 | ≤0.001 |
| Buss-Durkee Inventory | 41.8 | 12.4 | 36.9 | 11.5 | 1.45 | n.s. |
| Sensation Seeking Scale | 18.2 | 7.1 | 18.1 | 6.5 | <1 | n.s. |

[a] The number of self-mutilators for whom scores were available ranged from 19 to 26; the number of nonmutilators for whom scores were available ranged from 16 to 26.

[b] Two-tailed t test.

Self-mutilators scored significantly higher or almost significantly higher than control subjects on all but two of the 11 subscales of the Schedule for Interviewing Borderlines (table 2). Self-mutilators also had significantly greater total aggression than control subjects on the measure of history of aggression (table 2). Self-mutilators were significantly more antisocial as determined by their mean score on the MMPI psychopathic deviance subscale (table 2). Self-mutilators and control subjects did not differ significantly on the mean total Buss-Durkee Inventory score (table 2) or on any mean subscale score. There were no group differences for the mean total Sensation Seeking Scale score (table 2) or on any mean subscale score.

Within the self-mutilator group, correlations were computed between the degree of self-mutilation and all other indexes of psychopathology (a total of 36 scale and subscale correlations). Although we found no significant difference between the two groups in impulsivity as measured by the Schedule for Interviewing Borderlines subscale, there was a significant positive correlation between the degree of self-mutilation and impulsivity within the self-mutilator group (r=0.54, N=26, p≤0.01). The degree of self-mutilation was also significantly correlated with inappropriate chronic anger (r=0.43, N=26, p≤0.05) and with the somatic anxiety item (r=0.46, N=24, p≤0.05) but not with the psychic anxiety item (r=0.16, N=24, n.s.) of the chronic anxiety subscale (r=0.34, N=24, p≤0.10). There was a significant negative correlation between the degree of self-mutilation and Beck Hopelessness Scale score (r=–0.43, N=23, p≤0.05). There was a nonsignificant trend toward a positive correlation between the degree of self-mutilation and the aggression score (r=0.37, N=24, p≤0.08). No other correlations between degree of self-mutilation and measures of psychopathology approached significance. Aggression and impulsivity scores were significantly positively correlated (r=0.61, N=24, p≤0.01).

### *Biological Measures*

In the self-mutilator group, there was a significant negative correlation between the degree of self-mutilation and $B_{max}$ and between impulsivity and $B_{max}$ (table 3). Aggression did not significantly correlate with any of the serotonergic measures in the self-mutilator group (table 3).

In the control group and in the total study group no significant correlation was found between the serotonergic measures and impulsivity or aggression (table 3).

The mean CSF 5-HIAA levels for the self-mutilators and nonmutilators were 19.4 (SD=9.7) and 20.2 (SD=9.7), respectively (t<1, df=36, n.s.). The respective mean values of $B_{max}$ for the two groups were 861.2 (SD=423.6) and 1004.9 (SD=502.5) (t<1, df=29, n.s.), and the respective mean values of $K_d$ were 1.7 (SD=0.6) and 1.6 (SD=1.0) (t<1, df=29, n.s.). Thus, self-mutilators and control subjects did not differ from each other on any measure of serotonergic function.

## DISCUSSION

Our study resulted in the following significant findings: 1) self-mutilators had more severe character pathology than diagnostically matched nonmutilators, 2) there was a significant positive correlation between the degree of self-mutilation and impulsivity, chronic anger, and somatic anxiety, 3) there was a significant negative correlation between the degree of self-mutilation and $B_{max}$ and between impulsivity and $B_{max}$. Because the two groups did not differ diagnostically regarding affective and personality disorders or in their suicide history, these findings can be more confidently attributed to self-mutilation per se.

The results delineate the affective profile of self-mutilators as individuals who suffer from more depression than control subjects according to the Hamilton depression scale but not the Beck Depression Inventory but do not suffer from greater hopelessness. We might speculate that the significant negative correlation between the degree of self-mutilation and hopelessness lends support to the conceptualization of self-mutilation as an act of self-healing through the transient restoration of more hopeful affect. The more striking finding, however, is the greater dysphoric affect, with anxiety, anger, emptiness, and rejection sensitivity, that characterized our self-mutilator group. Mounting anxiety has been clinically described as an important predictor in the escalating phase before the act of self-mutilation. Mounting anxiety may be either a direct precipitant of self-mutilation or the final common pathway to a variety of thoughts, affects, and experiences that trigger self-mutilating behavior. Relief of mounting anxiety has been cited as a reason for self-mutilation in 35% (9), 45% (8), and 86% (7) of self-mutilators sampled in different studies. In our study, chronic somatic anxiety was significantly correlated with the degree of self-mutilation, and self-mutilators had greater anxiety than control subjects on the Schedule for Interviewing Borderlines and the Hamilton depression scale.

The contribution of poor impulse control to acts of self-mutilation is supported by our finding of a significant positive correlation between impulsivity and the degree of self-mutilation. However, impulsivity as measured by the Schedule for Interviewing Borderlines did not differ between self-mutilators and control subjects. Thus, what distinguishes self-mutilators is not their impulsivity, which they share with other individuals with severe personality disorders, but their greater aggression, which when combined with poor impulse control takes the form of self-mutilation rather than less aggressive impulsive behaviors assessed by the Schedule for Interviewing Borderlines, such as gambling, spending, promiscuity, overeating, and oversleeping.

This hypothesis is strongly supported by our finding of greater aggressive behavior, sociopathic tendencies, and chronic anger in the self-mutilators. Bennum (8) reported similar findings in a comparison of self-mutilators, nonmutilating depressed patients, and normal control subjects. Self-mutilators and depressed patients did not differ in overall Beck Depression Inventory scores, and both had greater depression than normal control subjects. However, self-mutilators had greater outwardly directed hostility than depressed patients, although they had comparable levels of inwardly directed hostility. Indeed, before and during the act of self-mutilation, 18%–45% of patients in various studies (7–9) reported anger toward themselves, and 10%–32% reported anger toward others. In our study group of self-mutilators, chronic inappropriate anger was significantly correlated with the degree of self-mutilation. It is notable that the two major affects that have previously been found to characterize patients' emotional states at the time of self-mutilation—anger and anxiety—were also found to be longstanding traits differentiating self-mutilators and nonmutilators in the current study.

Of note is the overall greater degree of psychopathology in the self-mutilator group with regard to multiple borderline traits compared with the control subjects matched for the presence and type of personality disorder. This could indicate that self-mutilation in itself may be a marker for more severe borderline character pathology and thus may have prognostic implications that extend beyond the treatment of the self-mutilative aspect per se. Alternatively, the combination of impulsivity and aggression and the variety of personality disorders characteristic of the self-mutilator group raise the argument that self-mutilation might best be viewed as a distinct axis I impulse control disorder, as intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania are currently viewed in *DSM-III-R* (27, 28). Furthermore, impulse control disorders could be subdivided into aggressive and nonaggressive types (e.g., self-mutilation and kleptomania, respectively). In this light, self-mutilation could be conceptualized as not only a symptom specific to borderline personality disorder but an impulsive syndrome that may be more common in but not limited to

**TABLE 3. Correlations Between Biological Variables and Self-Mutilation, Impulsivity, and Aggression in Subjects With Personality Disorders Who Were or Were Not Self-Mutilators[a]**

| | Correlation (r) | | |
|---|---|---|---|
| Variable | Self-Mutilators | Nonmutilators | Both Groups |
| CSF 5-HIAA | | | |
| Self-mutilation | 0.43 | | 0.1[illegible] |
| Impulsivity | 0.06 | –0.14 | –0.06 |
| Aggression | 0.20 | –0.17 | –0.0[illegible] |
| $B_{max}$ | | | |
| Self-mutilation | –0.57[b] | | –0.29 |
| Impulsivity | –0.61[b] | 0.16 | –0.14 |
| Aggression | –0.37 | –0.25 | –0.33 |
| $K_d$ | | | |
| Self-mutilation | 0.04 | | 0.04 |
| Impulsivity | 0.33 | –0.06 | 0.06 |
| Aggression | 0.29 | –0.22 | –0.03 |

[a] The number of self-mutilators for whom biological variables were obtained ranged from 13 to 17; the number of nonmutilators for whom the values were obtained ranged from 18 to 21.

[b] $p \leq 0.05$.

patients with borderline personality disorder, similar to substance abuse and bulimia.

From a biological perspective, our main finding was the significant negative correlation between degree of self-mutilation and imipramine binding and between impulsivity and imipramine binding. Platelets have been viewed as an analog of the serotonergic neuron because their uptake, storage, and release of serotonin are similar to those of the presynaptic neurons. A smaller number of imipramine binding sites has been reported in a variety of psychiatric conditions and may reflect central serotonergic dysfunction with reduced presynaptic serotonin release. A few studies have specifically linked this serotonergic index to disorders of aggression and impulsivity. Stoff et al. (16) found significantly fewer platelet imipramine binding sites in prepubertal children who had conduct disorders with or without attention deficit disorder with hyperactivity than in normal control subjects. Stoff et al. also found a significant negative correlation between binding sites and externalizing and aggressive behavior in adolescents who had histories of assaultive actions. Birmaher et al. (17) studied children who had conduct disorders with or without attention deficit disorder with hyperactivity but who did not have depression and suicidality and found an inverse correlation between impulsive, hostile, and aggressive behaviors and platelet imipramine binding sites. Similar to these two studies, our study links platelet imipramine binding to another form of aggressive and impulsive behavior, self-mutilation. The association between the degree of self-mutilation and imipramine binding in the absence of an absolute difference in serotonergic measures between self-mutilators and control subjects raises the issue of whether serotonergic dysfunction may be more important in terms of the severity of self-mutilation rather than the presence or absence of this behavior. Of interest, when we excluded all patients with histories of suicide attempts from both groups in order to control for the possibly confounding association between serotonin and suicide, the three self-mutilators had mean CSF 5-HIAA levels that were 44% lower (mean=16.7, SD=4.2) than those of the five non-mutilators (mean=30.1, SD=13.0). This relationship merits future investigation with larger samples.

In summary, our initial psychological results highlight the contribution of severe character pathology, impulsivity, aggression, anxiety, and anger to self-mutilating behavior. Our initial biological results indicate that serotonergic dysfunction may facilitate self-mutilation, as has been shown for other impulsive and aggressive behaviors. Our relatively small sample sizes, especially for the biological measures, as well as the mild to moderate mean frequency of self-mutilation in our patient group, may have limited the strength of our findings. Therefore, a prospective study of a larger group of subjects with more acute, severe, and frequent acts of self-mutilation, as well as development of a standardized instrument to operationally assess self-mutilation, are warranted to further enhance our understanding of self-mutilation from both a psychological and a biological perspective.

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# Prevalence of Mental Disorder in 88 Morbidly Obese Bariatric Clinic Patients

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*Objective: The authors sought to determine the association between mental disorder and morbid obesity, defined as weight at least 100% or 100 lb over ideal body weight. Method: Eighty-eight morbidly obese subjects who had come to a tertiary care center surgery clinic requesting vertical banded gastroplasty were systematically interviewed with the National Institute of Mental Health Diagnostic Interview Schedule (DIS) and the Structured Interview for DSM-III Personality Disorders. A comparison group of 76 psychiatrically normal subjects who were matched in age (within 5 years) and gender to the morbidly obese subjects were also interviewed. Results: Most of the morbidly obese subjects were women, were of low socioeconomic status as indicated by method of payment for medical care, weighed more than 300 lb, and had been obese for more than 14 years. The morbidly obese subjects were more likely than the comparison group to have a lifetime history of mood disorders, anxiety disorders, bulimia, and tobacco dependence. The morbidly obese subjects were also more likely to meet diagnostic criteria for one or more personality disorders. Conclusions: Substantial psychopathology exists in morbidly obese individuals requesting gastroplasty, a finding that has important clinical implications.*

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Morbid obesity, defined as weight at least 100% or 100 lb (45 kg) over ideal body weight, is a major health problem (1, 2). It is associated with substantial morbidity and excessive mortality as an established risk factor for cardiovascular, metabolic, neoplastic, and orthopedic conditions (1). Because of the relationship of morbid obesity to serious illness, attention has been focused on methods for producing weight loss. Conventional approaches for the management of obesity (e.g., dieting) have proven unsuccessful for the morbidly obese, leading to the development of surgical alternatives. Gastric restriction procedures, particularly vertical banded gastroplasty, have become the most common surgical procedures for the treatment of morbid obesity. In vertical banded gastroplasty, a small gastric pouch is created that physically limits the patient's caloric intake and gives the patient a sensation of satiety (2).

Despite renewed interest in the physiology, etiology, and treatment of obesity, little has been learned over the past two decades about its relationship to specific emotional disturbances. Studies of individuals with mild to moderate obesity suggest that they are no more likely than others to suffer from mental disorders (3). Studies of the morbidly obese, however, have been less conclusive. Since 1960, 15 articles (4–18) have reported rates of mental illness in morbidly obese individuals. The results varied markedly from one study to another for both rates and types of mental disorders. For instance, the rates for depression ranged from 4% to 80%, and the rates for personality disorder ranged from 15% to 83% (table 1). The 15 studies, along with the results of the present study, are summarized in table 1.

Castelnuovo-Tedesco (19) concluded in 1987 that although mild to moderate depression or personality disturbance was commonplace among the morbidly obese, severe psychopathology including "psychosis or crippling neurosis" rarely seemed to occur in this group. However, it is difficult to draw sound conclusions from the studies he reviewed because their methods differed substantially. All relevant studies are flawed to some extent. Other than our own current study, 12 of the 15 studies reviewed in table 1 specified criteria for morbid obesity (4, 5, 7, 8, 10, 11, 13–18), seven specified criteria for the diagnosis of mental disorders (12–18), three used standardized interviews or assessments (15, 17, 18), and one included a comparison group (17). Further, many of the studies used small and possibly biased groups of subjects. For instance, in one study (5), the subjects were seen in a psychosomatic

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**TABLE 1. Studies of Prevalence of Mental Disorders in the Morbidly Obese**

| Investigator | Year | Number of Subjects | Criteria for Obesity | Criteria for Mental Disorders | Interview Conducted[a] | Comparison Group | Recruitment of Subjects |
|---|---|---|---|---|---|---|---|
| Mendelson et al. (4) | 1961 | 25 | >30% above ideal body weight | None given | No | No | Medical/psychiatric clinic |
| Fink et al. (5) | 1962 | 31 | >50% above ideal body weight | None given | No | No | Psychosomatic clinic |
| Reivich et al. (6) | 1962 | 30 | None given | None given | No | No | Referral for psychiatric evaluation |
| Atkinson and Ringuette (7) | 1967 | 21 | >275 lb for women;<br>>300 lb for men | None given | No | No | — |
| Swanson and Dinello (8) | 1970 | 25 | >50% above ideal body weight | None given | No | No | Volunteers for metabolic study |
| Kalucy and Crisp (9) | 1974 | 20 | None given | None given | No | No | Bariatric clinic |
| Castelnuovo-Tedesco and Schiebel (10) | 1975 | 12 | >300 lb | None given | No | No | Bariatric clinic |
| Webb et al. (11) | 1976 | 70 | >100% above ideal body weight | None given | No | No | Preoperative gastric bypass patients |
| Wise and Fernandez (12) | 1979 | 24 | None given | Feighner | No | No | Bariatric clinic |
| Halmi et al. (13) | 1980 | 80 | >100% above ideal body weight | *DSM-III* | No | No | Bariatric clinic |
| Hutzler et al. (14) | 1981 | 102 | >100% above ideal body weight | *DSM-III* | No | No | Bariatric clinic |
| Gentry et al. (15) | 1984 | 33 | >100% above ideal body weight | Feighner | Yes | No | Bariatric clinic |
| Dubovsky et al. (16) | 1985–1986 | 52 | >100% above ideal body weight | *DSM-III* | No | No | Bariatric clinic |
| Black et al. (17) | 1989 | 38 | >100% above ideal body weight | *DSM-III* | Yes | Yes | Bariatric clinic |
| Larsen (18) | 1990 | 103 | 45 kg or 100% above ideal body weight | *DSM-III* | Yes | No | Bariatric clinic |
| Black et al. (this study) | 1992 | 88 | >100% above ideal body weight | *DSM-III* | Yes | Yes | Bariatric clinic |

[a] Personal interview or other standardized assessment.

[b] Any affective disorder.

clinic; in another (6), the subjects had all been referred for psychiatric evaluation.

With the shortcomings of these studies in mind, we set out to design a project to investigate the prevalence of psychopathology in the morbidly obese. The subjects were outpatients seen at our university's department of surgery for evaluation for vertical banded gastroplasty. Subjects were carefully assessed for both major mental disorders (*DSM-III* axis I) and personality disorders (*DSM-III* axis II) by using structured instruments of established reliability. We were interested in learning whether rates of major mental illnesses and personality disorders were greater among the morbidly obese than would be expected in the community.

**TABLE 1 (continued)**

| Mental Disorders | | | |
|---|---|---|---|
| Personality Disorders (%) | Depression (%) | Other or None | |
| | | Type | % |
| 56 | 4 | Cyclothymia | 4 |
| | | Schizophrenia | 4 |
| | | Anxiety | 4 |
| | | Organic | 4 |
| | | Alcoholism | 4 |
| | | No diagnosis | 24 |
| 55 | 58 | Schizophrenia | 10 |
| | | No diagnosis | 3 |
| 63 | 17 | Anxiety | 3 |
| | | No diagnosis | 13 |
| 67 | 62 | Anxiety | 24 |
| | | Conversion | 5 |
| | | Alcoholism | 5 |
| | | Psychophysiological | 5 |
| | | Schizophrenia | 5 |
| 40 | — | Alcoholism | 4 |
| — | 80 | Anxiety | 25 |
| | | Alcoholism | 20 |
| | | Drug | 10 |
| | | No diagnosis | 15 |
| 83 | 8 | — | |
| 83 | — | Psychoneurosis | 11 |
| | | Psychosis | 1 |
| | | No diagnosis | 9 |
| — | 8 | No diagnosis | 92 |
| — | 29 | "Axis I" | 48 |
| | | "Axis I and axis II" | 50 |
| | | No diagnosis | 50 |
| 15 | 13 | Marital problems | 10 |
| | | Alcoholism | 1 |
| | | Hysteria | 1 |
| | | Schizoaffective | 1 |
| | | No diagnosis | 58 |
| — | 12 | Alcoholism | 6 |
| | | Hysteria | 3 |
| | | Anxiety | 1 |
| | | Mental retardation | 1 |
| — | 69 | Alcoholism | 2 |
| | | Mental retardation | 2 |
| 40 | — | — | |
| 22 | 8[b] | Anxiety | 14 |
| | | Somatoform | 2 |
| | | Adjustment | 15 |
| | | Mental retardation | 1 |
| | | No diagnosis | 55 |
| 72 | 31[b] | Anxiety | 48 |
| | | Bulimia | 8 |
| | | Tobacco dependence | 41 |

It is important to understand the extent of psychopathology in the morbidly obese. The number of individuals undergoing vertical banded gastroplasty is substantial (12), and the presence of a psychiatric disorder may be associated with poor compliance with medical treatment and thus may impede postsurgical recovery. In addition, psychiatric disorder may contribute to poor outcome in terms of weight loss. By learning about preexisting psychiatric disorders, the treatment team is better prepared to modify its approach to improve compliance, reduce the number of complications, and, one hopes, to boost weight loss. Furthermore, if the mere presence of psychopathology is used to exclude patients from receiving vertical banded gastroplasty (as it has been used to exclude patients from receiving heart transplants [20]), then it behooves us to study correlations between mental disorder and outcome. We will present outcome data in subsequent reports.

## METHOD

### *Subjects*

Eighty-eight patients seen at our university's surgery clinic for consultation regarding vertical banded gastroplasty were recruited between January 1987 and June 1989. Patients were eligible for this study if they were at least 18 years old and at least 100% or 100 lb (45 kg) over their desirable weight according to actuarial tables (21). Patients with clinically apparent mental retardation or organic brain syndromes were not eligible for the study because these disorders complicate the assessment of other forms of psychopathology. No subjects were excluded on this basis, however.

Intake was not consecutive because our trained rater was not available to attend the bariatric clinic each week. However, over the 30-month recruitment period, only three individuals invited to participate refused to do so.

### *Assessments*

Morbidly obese subjects were invited to participate in a study of the "psychological characteristics or emotional adjustment of morbidly obese persons." After giving informed consent, subjects were evaluated by a trained rater using 1) the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (22), which has established adequate reliability for diagnosing major mental disorders according to *DSM-III* criteria, 2) an additional semistructured interview that we developed covering demographic and clinical information, such as family history and age at onset of obesity, and 3) the Personality Diagnostic Questionnaire (PDQ) (23), a self-report instrument used to assess *DSM-III* personality disorders. Starting in November of 1987, the Structured Interview for DSM-III Personality Disorders (24) was added to the assessment battery to provide a more thorough personality assessment. This instrument has shown adequate reliability for many of the *DSM-III* personality disorders.

### *Comparison Group*

Subjects used for comparison were recruited in the course of another study. As part of a family study of

**TABLE 2. Method of Medical Care Payment of 88 Morbidly Obese Subjects**

| Method of Payment | Number | Percent |
|---|---|---|
| Medicaid or Medicare | 40 | 45.5 |
| Public aid | 12 | 13.6 |
| Blue Cross/Blue Shield | 21 | 23.9 |
| Private insurance | 13 | 14.8 |
| Unknown | 2 | 2.3 |

obsessive-compulsive disorder, we identified 33 psychiatrically normal subjects who had been screened with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (25). We then systematically interviewed all available first-degree relatives (N=129) of these normal subjects using the DIS (22) and the Structured Interview for DSM-III Personality Disorders (24). These relatives made up a relatively unbiased community sample. From these 129 potential subjects, we identified 76 who were matched in age (within 5 years) and gender to the morbidly obese subjects.

### *Statistical Analysis*

Categorical data were analyzed by using the chi-square statistic and, when necessary, Fisher's exact test. We analyzed our continuous data by using the nonparametric Wilcoxon rank sum test. Odds ratios were calculated with 95% confidence intervals for individual diagnoses and diagnostic categories (26). The odds ratio is an estimate of the magnitude of the association between the presence of two characteristics, such as morbid obesity and major depression. For example, an odds ratio of 1 is interpreted as evidence of no association, but an odds ratio of 4.0 would indicate that subjects with morbid obesity would be four times more likely than comparison subjects to have major depression. We report crude (i.e., unadjusted for age and gender) odds radios because our data showed that these variables did not confound the association between obesity and mental disorder.

## RESULTS

Eighty-eight subjects with morbid obesity were included in the study; 18 (20.5%) were men, and 70 (79.5%) were women. Their mean age was 36.1 years (SD=10.3); men had a mean age of 34.2 (SD=10.9), and women had a mean age of 36.6 (SD=10.2). Of the 76 subjects in the comparison group, 18 (23.7%) were men and 58 (76.3%) were women; their mean age was 36.5 (SD=11.2). The age and gender distributions of the comparison subjects were comparable to those of the morbidly obese subjects. Eighty-six (97.7%) of the morbidly obese subjects were white, and two (2.3%) of the obese subjects were black.

The baseline mean weight of the morbidly obese subjects was 141.3 kg (SD=28.3); the mean weight of the men was 170.8 kg (SD=26.8), and the mean weight of the women was 133.5 kg (SD=23.3). The mean age at onset of obesity for the morbidly obese subjects was 11.5 (SD=9.9) years; mean age at onset for the men was 8.9 (SD=7.5), and mean age at onset for the women was 11.8 (SD=10.3). The methods of payment for medical care of the morbidly obese subjects are presented in table 2.

The lifetime prevalence of psychiatric disorders in the morbidly obese subjects and the comparison subjects is presented in table 3. These percentages are based on definite cases of the disorders according to DIS results; subjects could qualify for more than one diagnosis. The morbidly obese subjects had a significantly higher prevalence of mood disorders (especially major depression), anxiety disorders (especially agoraphobia, simple phobia, and posttraumatic stress disorder [PTSD]), bulimia, and tobacco dependence than the comparison subjects. If all disorders measured by the DIS are totaled, 84% of the morbidly obese subjects and 59% of the comparison group met criteria for at least one disorder.

The obese subjects were significantly more likely to have one or more psychiatric disorders (table 4). They had a mean of 2.1 disorders (SD=1.5) and a median of 2, compared with a mean of 0.9 (SD=1.0) and a median of 1 for the comparison subjects (Z=–5.63, p=0.000000009, Wilcoxon rank sum test).

The frequency distributions of personality disorders for the two groups are presented in table 5. The obese subjects for this analysis included only the 46 patients who were given the Structured Interview for DSM-III Personality Disorders. Their mean age was 37.0 years (SD=10.1), and 37 (80.4%) were women; their age and gender distributions were comparable to those of the morbidly obese group as a whole. Frequencies were based on definite diagnoses of the disorders according to the Structured Interview for DSM-III Personality Disorders results; subjects could qualify for more than one personality disorder diagnosis. Morbidly obese subjects were significantly more likely than subjects in the comparison group to manifest "eccentric" (cluster A), "dramatic" (cluster B) (except for narcissistic), and "anxious" (cluster C) (especially avoidant and passive-aggressive) personality disorders.

The morbidly obese subjects were also more likely than comparison subjects to exhibit symptoms of personality disorder and to meet criteria for more than one disorder according to the Structured Interview for DSM-III Personality Disorders (table 6). In fact, 72% (N=33) of the 46 of morbidly obese subjects met criteria for at least one personality disorder, compared with only 37% (N=28) of the 76 comparison subjects. The 46 morbidly obese subjects had a mean of 27.2 symptoms (SD=12.9) and a median of 29, compared with a mean of 14.2 (SD=8.8) and a median of 11.5 for the comparison subjects (Z=5.41, p=0.00000003, Wilcoxon rank sum test). They had a mean of 1.7 personality disorders (SD=1.5) and a median of 1.5, compared with a mean of 0.6 (SD=0.9) and a median of 0 for the comparison subjects (Z=4.58, p=0.000002, Wilcoxon Rank Sum test).

**TABLE 3. Lifetime Prevalence of Major Mental Disorders in Morbidly Obese Subjects and Comparison Subjects**

| | Morbidly Obese Subjects (N=88) | | Comparison Subjects (N=76) | | | | |
|---|---|---|---|---|---|---|---|
| Diagnosis | N | % | N | % | Odds Ratio | 95% Confidence Interval | Significance[a] |
| Mood disorders | | | | | | | |
| Mania | 3 | 3.4 | 0 | 0.0 | | | |
| Major depression | 17 | 19.3 | 4 | 5.3 | 4.3 | 1.4–13.4 | $\chi^2=7.2$, p=0.007 |
| Dysthymia | 7 | 8.0 | 3 | 4.0 | 2.1 | 0.5–8.4 | n.s. |
| Atypical bipolar disorder | 1 | 1.1 | 0 | 0.0 | | | |
| Any affective disorder | 27 | 30.7 | 7 | 9.2 | 4.4 | 1.8–10.7 | $\chi^2=11.4$, p=0.0007 |
| Substance abuse | | | | | | | |
| Alcoholic disorder | 20 | 22.7 | 16 | 21.1 | 1.1 | 0.5–2.3 | n.s. |
| Drug disorder | 2 | 2.3 | 4 | 5.3 | 0.4 | 0.1–2.4 | n.s. |
| Any substance use disorder | 20 | 22.7 | 18 | 23.7 | 0.9 | 0.5–2.0 | n.s. |
| Anxiety disorders | | | | | | | |
| Panic | 3 | 3.4 | 0 | 0.0 | | | |
| Obsessive-compulsive disorder | 3 | 3.4 | 2 | 2.6 | 1.3 | 0.2–8.0 | n.s. |
| Agoraphobia | 10 | 11.4 | 2 | 2.6 | 4.7 | 1.0–22.4 | $\chi^2=4.6$, p=0.03 |
| Social phobia | 5 | 5.7 | 2 | 2.6 | 2.2 | 0.4–11.8 | n.s. |
| Simple phobia | 20 | 22.7 | 4 | 5.3 | 5.3 | 1.7–16.3 | $\chi^2=10.0$, p=0.002 |
| PTSD | 9 | 10.2 | 1 | 1.3 | 8.5 | 1.1–69.1 | p=0.02 |
| Generalized anxiety disorder | 18 | 20.5 | 9 | 11.8 | 1.9 | 0.8–4.6 | n.s. |
| Any anxiety disorder | 42 | 47.7 | 12 | 15.8 | 4.9 | 2.3–10.3 | $\chi^2=18.8$, p=0.00001 |
| Bulimia | 7 | 8.0 | 1 | 1.3 | 6.5 | 0.8–53.9 | p=0.05[b] |
| Tobacco dependence | 36 | 40.9 | 16 | 21.1 | 2.8 | 1.4–5.7 | $\chi^2=7.4$, p=0.007 |
| Any disorder | 74 | 84.1 | 45 | 59.2 | 3.6 | 1.8–7.6 | $\chi^2=12.7$, p=0.0004 |

[a] For chi-square tests, df=1.

[b] One-tailed Fisher's exact test.

## DISCUSSION

Several conclusions can be drawn about the morbidly obese subjects who came to our bariatric clinic. Most were women. They tended to be of low socioeconomic status as indicated by the method of payment for medical care, they had been obese for more than 14 years, and they weighed, on average, more than 140 kg (308 lb). Careful assessment showed that the morbidly obese subjects had higher rates of mood disorders, anxiety disorders, bulimia, tobacco dependence, and personality disorders than a comparison group from the community. These findings were supported by the finding of an excess number of DIS and Structured Interview for DSM-III Personality Disorders diagnoses in the morbidly obese. Our findings directly contradict those of Stunkard et al. (1), who concluded that the prevalence of psychiatric disorders among morbidly obese individuals does not significantly differ from that in the general population. Their conclusion was based on a review of two papers (13, 15), neither of which was designed to compare prevalence of mental disorder in the morbidly obese with community norms. In fact, our morbidly obese subjects clearly experienced substantial and excessive psychological distress.

Although experts agree that a distorted body image and preoccupation with weight are cardinal features of morbidly obese patients, there has been little consensus on the degree and type of emotional pathology seen in these patients (1, 19). Early studies emphasized that although obese individuals were free of severe psychopathology (e.g., psychosis), they were often prone to neurosis or personality disturbances believed by psychodynamically oriented clinicians to result from oral fixation or from regression after failure to master oedipal situations (19). More recent studies have focused on prevalence rates of specific mental illnesses. Perhaps reflecting the ease with which this particular group can be studied, most reports on the psychological state of the morbidly obese have been carried out on patients who are seeking surgical treatments of obesity or are referred for such treatments.

**TABLE 4. Number of Lifetime *DSM-III* Disorders in Morbidly Obese Subjects and Comparison Subjects[a]**

| | Morbidly Obese Subjects (N=88) | | Comparison Subjects (N=76) | |
|---|---|---|---|---|
| Number of Disorders | N | % | N | % |
| None | 14 | 15.9 | 31 | 40.8 |
| One | 19 | 21.6 | 32 | 42.1 |
| More than one | 55 | 62.5 | 13 | 17.1 |

[a] $\chi^2=35.0$, df=2, p=0.000000003.

Although our study found a high prevalence of specific mental disorders in the morbidly obese, it cannot answer the question of why these patients suffer psychological distress. It is possible that the morbidly obese come from families genetically loaded for mental illness and that this genetic vulnerability (or the conse-

**TABLE 5. Frequency of Personality Disorders Diagnosed With the Structured Interview for DSM-III Personality Disorders in Morbidly Obese Subjects and Comparison Subjects**

| Personality Disorder Diagnosis | Morbidly Obese Subjects (N=46) | | Comparison Subjects (N=76) | | Odds Ratio | 95% Confidence Interval | Significance[a] |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| Eccentric cluster | | | | | | | |
| Any disorder | 8 | 17.4 | 3 | 3.9 | 5.1 | 1.3–20.4 | p=0.02[b] |
| Paranoid | 3 | 6.5 | 1 | 1.3 | 5.2 | 0.5–51.9 | n.s. |
| Schizoid | 0 | 0.0 | 0 | 0.0 | | | |
| Schizotypal | 5 | 10.9 | 2 | 2.6 | 4.5 | 0.8–24.3 | n.s. |
| Dramatic cluster | | | | | | | |
| Any disorder | 20 | 43.5 | 5 | 6.6 | 10.9 | 3.7–32.1 | $\chi^2$=23.9, p=0.000001 |
| Histrionic | 15 | 32.6 | 3 | 3.9 | 11.8 | 3.2–43.6 | $\chi^2$=18.7, p=0.00002 |
| Narcissistic | 0 | 0.0 | 0 | 0.0 | | | |
| Antisocial | 4 | 8.7 | 0 | 0.0 | | | |
| Borderline | 14 | 30.4 | 3 | 3.9 | 10.6 | 2.9–39.6 | $\chi^2$=16.8, p=0.00004 |
| Anxious cluster | | | | | | | |
| Any disorder | 22 | 47.8 | 15 | 19.7 | 3.7 | 1.7–8.4 | $\chi^2$=10.7, p=0.001 |
| Avoidant | 7 | 15.2 | 3 | 3.9 | 4.4 | 1.1–17.8 | p=0.04[b] |
| Dependent | 6 | 13.0 | 3 | 3.9 | 3.7 | 0.9–15.4 | n.s. |
| Compulsive | 6 | 13.0 | 8 | 10.5 | 1.3 | 0.4–3.9 | n.s. |
| Passive-aggressive | 14 | 30.4 | 9 | 11.8 | 3.3 | 1.3–8.3 | $\chi^2$=6.5, p=0.01 |

[a] For chi-square tests, df=1.

[b] One-tailed Fisher's exact test.

**TABLE 6. Number of Personality Disorders Diagnosed With the Structured Interview for DSM-III Personality Disorders in Morbidly Obese Subjects and Comparison Subjects[a]**

| Number of Disorders | Morbidly Obese Subjects (N=46) | | Comparison Subjects (N=76) | |
|---|---|---|---|---|
| | N | % | N | % |
| None | 13 | 28.3 | 48 | 63.2 |
| One | 10 | 21.7 | 19 | 25.0 |
| More than one | 23 | 50.0 | 9 | 11.8 |

[a] $\chi^2$=23.0, df=2, p=0.000002.

quence of growing up in a disorganized and abusive home as a result of parental mental illness) leads to the development of emotional disorders such as major depression. There is evidence that the families of obese individuals (not necessarily morbidly obese individuals) are emotionally disturbed (27, 28). Alternatively, morbid obesity may itself lead to depression, anxiety, or other disturbances brought on by the considerable ostracism morbidly obese individuals experience. In a society that values youth, beauty, and slimness, the obese are made to feel unattractive and inadequate. It is possible that a combination of genetic and social influences have jointly led to these emotional disorders.

Specific anxiety disorders that were more frequent in the morbidly obese subjects included agoraphobia, simple phobia, and PTSD. It is tempting to speculate that morbidly obese individuals develop phobic avoidance in response to social cues such as stares or whispered comments, but other factors may be operating as well. PTSD, uncommon in the general population (29), usually results (in women) from the effects of a violent assault or rape. All morbidly obese subjects meeting criteria for PTSD in our study were women, leading us to speculate that morbidly obese women suffer from substantial physical or sexual abuse. This abuse may be interpreted as an extreme form of the social stigmatization that they suffer as a consequence of their obesity. On the other hand, victims of abuse or trauma may turn to food for solace.

Our findings on personality disorders based on the Structured Interview for DSM-III Personality Disorders support an earlier pilot study (17). In that report, personality was assessed in 38 morbidly obese individuals (a subset of the current sample) by using a self-report instrument, the PDQ. Contrary to the findings of earlier studies (7, 10, 14), dependent and passive-aggressive personality were not the most frequent disorders. Our pilot study showed that eccentric and dramatic cluster disorders, especially borderline personality, were the most common personality disturbances in morbidly obese subjects. In the current study, all three personality disorder clusters were significantly more frequent in the morbidly obese than in the comparison group, especially the eccentric and dramatic clusters. Since early investigators tended to base their diagnoses on clinical interviews, and all predated *DSM-III*, direct comparisons with our findings are inappropriate.

As we have pointed out elsewhere (17), the distorted self-image and identity that many morbidly obese individuals suffer from could lead to an endorsement of the criteria for a personality disorder. For example, according to *DSM-III-R* criteria, the morbidly obese may understandably feel a tendency to "read hidden . . . meanings into benign remarks" (criteria for paranoid personality), to have "extreme discomfort in social situations" (criteria for schizotypal personality), to choose "solitary activities" (criteria for schizoid personality), to have "impulsiveness in . . . areas that are self-damaging" such as binge eating and "persistent identity disturbances" (criteria for borderline personality), or be "easily hurt by criticism or disapproval" (criteria for avoidant personality). Whether this endorsement of criteria reflects enduring maladjustment, which is expected in a personality disorder, or represents a transient disturbance associated with the morbid obesity that will correct with weight loss is open to question. Therefore, it will be important to learn whether weight loss following vertical banded gastroplasty leads to the abandonment of abnormal personality traits and is associated with a concomitant improvement in PDQ or Structured Interview for DSM-III Personality Disorders scores. Some believe that the endorsement of certain criteria is a reflection of the morbid obesity rather than of the individual. However, if diagnostic criteria are to have any meaning, they need to be applied regardless of presumed etiology.

Other disorders that were more frequent than expected in our morbidly obese subjects were bulimia and tobacco dependence. Although morbid obesity is not recognized as an eating disorder in *DSM-III-R*, it shares certain similarities with bulimia nervosa (30), such as a lack of control over eating and a preoccupation with body image. The finding of excess tobacco dependence may be confounded by social class because, like our morbidly obese subjects, smokers are predominantly from the lower social classes (31). Possibly, the obese take up smoking cigarettes as a substitute for eating, only to find themselves addicted to them.

Although the data showed that the morbidly obese suffer more psychopathology than a comparison group in a Midwest community, these findings cannot tell us whether the pattern of psychopathology is unique to the morbidly obese. A surgical or medically ill comparison group could help to solve that question. Further, the findings may apply only to morbidly obese individuals who seek surgery, since those who do not seek surgery may have rates of mental disorder no different from what would be expected in the general population. However, the vertical banded gastroplasty population is substantial, so our data remain important even if they apply only to that specific group of patients.

Additional limitations of our study need to be acknowledged. Although the study group was relatively large, the low base rate of most mental disorders means that some of the individual cell samples (e.g., subjects with panic disorder) were small. A larger study group would have reduced the possibility of a type II error (i.e., accepting the null hypothesis when it is false) and helped to minimize the lack of precision of the odds ratios indicated by their wide confidence intervals. Error could also have arisen from rater bias or from errors in the administration of the assessment instruments, since the data reported came primarily from interviews. Although the DIS and the Structured Interview for DSM-III Personality Disorders are fully structured, and the same person interviewed both morbidly obese and comparison subjects, the rater was aware of the study objectives. Future investigations should be designed to ensure that raters are blind to study purposes.

Most of our patients were white women of low socioeconomic status who came to a tertiary care facility for vertical banded gastroplasty. Our subjects may therefore not be representative of morbidly obese individuals in general or of those who seek treatment at other centers. However, the sociodemographic profile of our study subjects was similar to that reported by other researchers in a tertiary care setting (14).

It might be argued that the way the comparison group was selected helped to eliminate mentally ill individuals, thereby exaggerating the differences between the groups. In fact, the frequency of mental disorders in the comparison group was comparable to national rates reported in the Epidemiologic Catchment Area study (32), a finding that supports their validity.

The effect of psychiatric history and of specific psychiatric disorders on the outcome of patients who have bariatric surgery remains to be determined. Follow-up of our study subjects and future studies of bariatric patients should provide answers to these questions.

The findings from the current study may help lead to a better understanding of and care for morbidly obese patients. Studies such as ours may eventually help to match patients with obesity treatments and aid in the design of follow-up plans tailored to individual needs. Improvements in care would likely help to boost compliance, minimize complications, and maximize weight loss. These advances could include medication regimens, educational and counseling efforts tailored to specific psychiatric disorders, frequent clinic visits to provide support and encouragement, and appropriate psychiatric referral.

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# Patients Who Use Drugs During Inpatient Substance Abuse Treatment

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*Objective: Drug use by patients during inpatient substance abuse treatment is frequently a cause of premature hospital discharge. The authors examined the histories of patients who used drugs while in inpatient substance abuse treatment, the methods used to detect drug use, and the temporal relationship of drug use episodes. Method: The authors reviewed the charts of patients admitted consecutively to an inpatient substance abuse treatment unit between 1981 and 1988. Of 729 patients, 42 were found to have used drugs while receiving inpatient treatment. The diagnoses and clinical histories of these 42 patients were compared with those of all other patients. Methods of detection and circumstances of drug use were recorded, and drug use episodes were plotted on a time line that was examined for temporal clustering. Results: Significantly more of the patients who used drugs during inpatient substance abuse treatment had primarily used heroin or methadone before treatment. Random urine screens, self-report, and staff observation together detected approximately 85% of the patients who used drugs during treatment. Episodes of drug use did cluster in time, but within clusters the hospital stays of the patients who used drugs did not necessarily overlap. Conclusions: Temporal clustering of drug use episodes may occur because drug use by one patient heralds drug availability and stimulates craving in other inpatients. Clinicians should be aware that one episode of drug use may be followed by others. Multiple detection methods, including random comprehensive urine screens, should be used to test for drug use on inpatient units.*
(Am J Psychiatry 1992; 149:235–239)

Drug use by patients during inpatient substance abuse treatment is the reason many patients are prematurely discharged from the hospital or drop out of treatment (1, 2). Although numerous studies have investigated the characteristics of patients who are discharged against medical advice (3–11) or drop out of drug abuse treatment (12–18), to our knowledge only one previous study (19) has examined drug use among inpatients in drug abuse treatment facilities, and that study investigated only cocaine use. We retrospectively reviewed data collected over 8 years and identified all patients on an inpatient substance abuse unit who used drugs during their treatment. The study was done to answer the following questions: 1) Were there any features among the patients' clinical, diagnostic, and substance abuse histories that characterized patients who used drugs while in inpatient substance abuse treatment? 2) Were the episodes of drug use related to each other in time? and 3) Which method was most effective in detecting drug use during inpatient substance abuse treatment?

## METHOD

### *Setting and Subjects*

We collected data on 729 patients admitted consecutively between 1981 and 1988 to an alcohol and drug abuse treatment unit in an urban private, nonprofit psychiatric hospital. The majority of patients were white and from middle and upper-middle socioeconomic levels. From 1981 to 1985 the unit treated only patients with primary drug dependence. In January 1986 the unit also began accepting patients with primary alcoholism, who previously had been treated on a separate alcoholism unit in the hospital.

Patients admitted to the unit participated in a multidis-

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**TABLE 1. Characteristics of Patients Who Did and Did Not Use Drugs During Inpatient Substance Abuse Treatment**

| Variable | Users | | Abstainers | | Chi-Square Analysis | |
|---|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ (df=1) | p |
| Sex | | | | | 0.72 | 0.50 |
| Male | 32 | 76 | 472 | 69 | | |
| Female | 10 | 24 | 215 | 31 | | |
| Total | 42 | 100 | 687 | 100 | | |
| Marital status | | | | | 0.77 | 0.50 |
| Married | 12 | 30 | 244 | 36 | | |
| Unmarried | 28 | 70 | 443 | 64 | | |
| Total | 40 | 100 | 687 | 100 | | |
| Employment | | | | | 2.00 | 0.50 |
| Employed | 33 | 80 | 407 | 69 | | |
| Unemployed | 8 | 20 | 186 | 31 | | |
| Total | 41 | 100 | 593 | 100 | | |

ciplinary substance abuse treatment program; the average length of stay was approximately 4 weeks. Supervised random urine toxicologic screens were obtained at least three times a week to ensure drug-free status throughout this period. The initial analysis of urine samples was by means of the enzyme-multiplied immunoassay technique (EMIT). The presence of drugs was confirmed with gas chromatography/mass spectrometry.

We reviewed hospital records to identify all patients who had brought drugs onto the unit, used drugs on the unit, or used drugs while on passes during their hospital stays. Virtually all such patients were either discharged or transferred to other treatment settings after discovery of their drug use.

### Data Collection

One of the physician investigators (S.F.G.) used a standardized chart audit form to collect the following information about the episodes of drug use during treatment: 1) type of drug used, 2) date of drug use, 3) whether the drug was used in the presence of other patients, and 4) method of detection.

The patients identified as having used drugs were compared with all other patients admitted to the unit on several sociodemographic, clinical, and substance abuse history variables that were routinely collected at admission with a 287-item self-administered questionnaire (20). The drug users' admission scores on the Social Adjustment Scale (21), revised 90-item Symptom Checklist (SCL-90-R) (22), Hamilton Rating Scale for Depression (23), and Beck Depression Inventory (24) were also compared with the scores of all other patients admitted to the unit.

For patients who had abused multiple substances before admission, we defined the primary drug of abuse as the drug that caused the greatest difficulties for the patient before admission. This was determined through clinical interview of the patient by the unit psychiatrist, the patient's response on a structured substance abuse history questionnaire, and information about the patient gathered from family members by the unit's social workers.

On the basis of repeated clinical interviews and observation of the patients' behavior on the unit, diagnoses based on *DSM-III* criteria were made at discharge by one of us (R.D.W.). An independent diagnostic assessment was carried out by a second psychiatrist, who was not involved with the research and who met with the patient three to four times each week throughout the hospital stay. When the two diagnoses differed, a consensus diagnosis was made, and only one diagnosis was recorded. Because of the difficulty in evaluating past psychiatric symptoms in the context of concurrent heavy drug use, a patient received an axis I diagnosis other than substance abuse only if he or she were currently ill and had previously fulfilled the diagnostic criteria for that disorder while drug free. Antisocial personality disorder was the only axis II disorder assessed because of the particular difficulty inherent in distinguishing between addiction-related behaviors and enduring personality characteristics. The reliability and validity of the antisocial personality disorder diagnosis have been rigorously tested (25), and the inclusion of age at onset in the diagnostic criteria helps distinguish symptoms of this disorder from behavior related to drug abuse.

### Data Analysis

Statistical significance was determined with the chi-square test for categorical data. A two-tailed Student's t test for independent samples was used for comparison of means. Episodes of drug use during treatment were plotted on a time line that was examined for apparent clustering of data points. The apparent clusters were then analyzed by using a Poisson distribution (26, 27) to estimate expected rates of drug use for each 3-month interval.

## RESULTS

Of the 729 patients admitted consecutively to the inpatient substance abuse unit, 42 patients (5.8%) used drugs during inpatient treatment. The sex, marital status, and employment status of these patients and those who did not use drugs during treatment are presented in table 1. The two groups did not differ significantly on any of these three variables. However, the mean age of the drug users (mean=29.8 years, SD=5.9) was significantly lower than that of the patients who did not use drugs (mean=31.8 years, SD=8.2) ($t=2.05$, $df=52.05$, $p \le 0.005$).

Among the total group of patients admitted to the alcohol and drug abuse treatment unit during the study period, the primary drugs of abuse were opioids for 34% of the patients, cocaine for 27%, alcohol for 12%, marijuana for 4%, benzodiazepines for 3%, and other drugs for 20%. As shown in table 2, the percentage of patients for whom opioids, particularly heroin and

**TABLE 2. Primary Pretreatment Drugs of Abuse for Patients Who Did and Did Not Use Drugs During Inpatient Substance Abuse Treatment**

| Primary Drug of Abuse Before Treatment | Users (N=42) | | Abstainers (N=687) | | Chi-Square Analysis | |
|---|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ (df=1) | p |
| Opioid | 26 | 62 | 222 | 32 | 14.15 | 0.005 |
| Heroin and/or methadone | 18 | 43 | 124 | 18 | 13.98 | 0.001 |
| Other | 8 | 19 | 98 | 14 | 0.39 | 0.70 |
| Cocaine | 7 | 16 | 192 | 28 | 3.13 | 0.10 |
| Other drug | 7 | 17 | 189 | 28 | 2.95 | 0.10 |
| Alcohol | 2 | 5 | 84 | 12 | 2.89 | 0.10 |

methadone, were the primary drugs of abuse was significantly higher among the patients who used drugs during treatment than among the patients who did not.

When we examined the data on substance abuse history, social adjustment, and psychiatric symptoms, we found that the mean age at first heavy drug use was lower among the patients who used drugs during treatment (mean=21.7 years, SD=3.9) than among the patients who did not (mean=23.8 years, SD=7.8) (t=2.34, df=26.72, $p \leq 0.03$). There were no differences between the two groups on any measure of current psychiatric symptoms or social adjustment. Twenty-three of the 42 drug users stayed in the hospital long enough for a diagnostic evaluation to be completed. The diagnosis of antisocial personality disorder was twice as common among this group as among the abstainers (35% and 16%, respectively; $\chi^2$=6.95, df=1, $p \leq 0.01$).

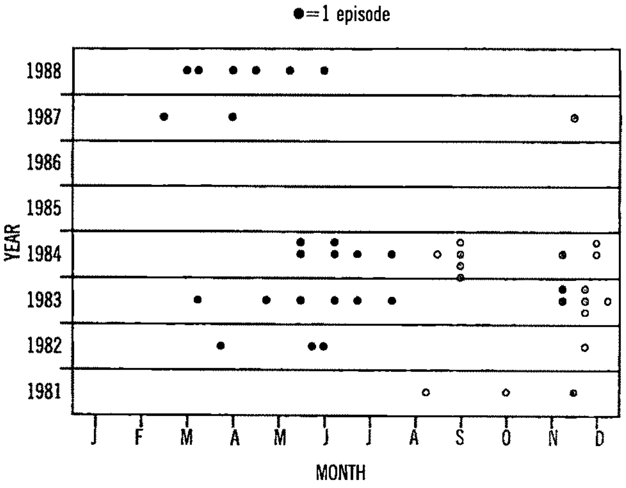
In examining patterns of drug use during treatment, we found that more than one-half of the drug users (N=23, 53%) used drugs that were not their primary drugs of abuse before admission. Drug use was initially detected by a random urine toxicologic screen in 38% of the cases (N=16), by staff observation that triggered a urine screen in 26% (N=11), by the patient's telling staff in 21% (N=9), and by reports from other patients in 10% (N=4). In two cases, it was not clear which method of detection was used. Of the 33 patients whose drug use was discovered by means other than their own admission, 19 patients (58%) admitted their drug use once confronted by staff.

Although no individual patient used drugs with any other individual patient during treatment, the episodes of drug use did cluster in time, as illustrated by figure 1. A Poisson analysis of the expected versus observed episodes demonstrated that the clustering was not attributable to chance alone ($\chi^2$=19.78, df=3, $p \leq 0.0002$). However, within clusters the hospital stays of the patients who used drugs did not necessarily overlap.

## DISCUSSION

Our findings suggest that for our subjects primary opioid abuse, especially heroin or methadone abuse, was a risk factor for drug use during inpatient treatment. Although the users during treatment were significantly younger at the time of treatment and at onset of drug abuse, the actual differences were probably too small to be clinically significant. The diagnosis of antisocial personality disorder was also more prevalent among those who used drugs during treatment.

**FIGURE 1. Temporal Distribution of Episodes of Drug Use by Patients During Inpatient Substance Abuse Treatment Over 8 Years**



In addition to these individual patient characteristics, we noted that the episodes of drug use on the substance abuse treatment unit tended to cluster in time. Interestingly, in each cluster the hospital stays of the inpatients who used drugs during treatment did not necessarily overlap with one another, and no patient who used drugs during treatment did so with another patient. This clustering was, therefore, not solely the result of direct transmission of drugs from one patient to another. Rather, a history of recent drug use on the unit served as a risk factor for drug use by other patients on the unit. Our findings are consistent with observations by Meyer and Mirin (28), who noted that drug craving on a heroin research ward was highly correlated with the subjects' perception of drug availability. In our study, the discussions by patients and staff about a former inpatient's relapse on the unit may have heralded drug availability to other inpatients, thus stimulating craving and leading to additional episodes of drug use on the unit.

Magura et al. (29) noted the complementary nature of self-report and urine screens in detecting illicit drug use in outpatient methadone treatment programs. Our results suggest that in inpatient substance abuse treatment staff observation is a third important method of detection. In fact, the three methods—supervised random urine screens, patient self-report, and staff observation—were complementary, together detecting approximately 85% of the patients who used drugs during treatment.

It is noteworthy that more than one-half of the patients who used drugs during treatment used substances other than their primary drugs of abuse. This argues for the use of comprehensive toxicologic screens for detection of drug use during treatment, rather than testing urine samples for only the patient's primary substance of abuse.

This study has several limitations. In an attempt to distinguish between coexisting psychopathology and the sequelae of drug abuse, we used two clinicians and multiple interviews to establish a consensus diagnosis, also using longitudinal clinical observations and historical data gathered from family members. Our diagnostic method has both strengths and weaknesses; an extended observation period, coupled with multiple sources of data, has been found to enhance validity in research (30–32). In addition, despite the evidence supporting the general utility of structured interviews, such as the Diagnostic Interview Schedule (33) and the Schedule for Affective Disorders and Schizophrenia (34), several studies (35–37) have shown the limitations of these instruments in the diagnosis of psychiatric disorders in substance abusers. However, because clinical interviews are less structured and may be less comprehensive than standardized instruments, we may have underdiagnosed some disorders.

Because of inadequate information, diagnoses other than substance abuse were made for only a limited number of the patients who used drugs during treatment, thus making our comparison with the abstainers potentially less reliable. Because diagnoses were made at discharge, after the detection of inpatient drug use, it is possible that the diagnosis of antisocial personality disorder in particular was subject to rater bias; this would lead to an overestimation of antisocial personality disorder in those who used drugs during treatment. The possibility of false positive urine tests in our study is remote because we used gas chromatography/mass spectrometry to confirm positive screens (38, 39). Finally, the results of this study may not be generalizable to groups whose socioeconomic characteristics, distribution of drugs of choice, or treatment setting differ substantially from those of our subjects.

These results do suggest that it is important to use multiple, complementary methods to detect drug use during treatment. They should include supervised random urine screens, staff observation, and patient self-report. The urine screen should be comprehensive and not limited to the primary drug of abuse. For patients addicted to a variety of substances, dependence on heroin or methadone may be a risk factor for drug use during inpatient treatment. Finally, clinicians should be advised that one episode of drug use on an inpatient substance abuse unit may be followed by others.

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# Now Is the Time to Retire the Term "Organic Mental Disorders"

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*The organic/nonorganic distinction in contemporary classifications of mental disorders such as* DSM-III *and* DSM-III-R *has important prognostic and treatment implications, because it directs the clinician to pay special attention to the possibility of an underlying "physical" disorder as the cause of the mental disturbance. However, the term "organic" raises serious and intractable problems, since the connotative meaning of the term always returns to its historical roots, which imply an outmoded functional/structural, psychological/biological, and mind/body dualism. The authors present a proposal being considered for* DSM-IV *that would eliminate the term "organic" and reorganize the classification of organic mental disorders. Disorders previously referred to as "organic mental disorders" would be renamed as either "secondary disorders" (if they are due to "physical" disorders) or "substance-induced disorders." The entire classification of mental disorders would be reorganized to distribute the secondary and substance-induced disorders into the major groups with which they share phenomenology. The traditional organic mental disorders—delirium, dementia, and amnestic disorder—would be grouped together under the rubric of "cognitive impairment disorders." While acknowledging problems with the suggested new terminology and reorganization of the classification, the authors argue that the potential benefits of the proposal for clarity and for facilitating differential diagnosis justify putting to rest the familiar but now anachronistic term "organic mental disorders."*

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> The antithesis between "organic" and "functional" disease still lingers at the bedside and in medical literature, though it is transparently false and has been abandoned long since by all contemplative minds.
>
> —S.A.K. Wilson, discoverer of Wilson's disease, as quoted by Reynolds (1)

The concept that certain "mental" syndromes could result from recognizable "physical" disorders or drug use can be traced back to the formal beginnings of Western medicine. Both Greek and Roman physicians observed that agitated mental disorders could be caused by fevers (e.g., the "phrenitis" of Hippocrates) or drugs (e.g., the "delirium due to alcohol or drugs" of Aretaeus) (2–4). The modern etiologic distinction between organic (physical) and functional (psychological) did not, however, enter psychiatric theorizing until the late seventeenth century, with the widespread acceptance of the Cartesian mind/body duality (4). The subsequent popularity of the organic/functional dichotomy reflected the two great divergent trends in psychiatry during the later part of the nineteenth century: 1) the newly emerging "brain psychiatry" fueled by the dramatic increase in knowledge of the anatomy and pathology of the human CNS and 2) an increasing interest and emphasis on mental phenomena and the unconscious in the etiology of mental illness, as exemplified by the work of Pierre Janet and, later, Freud (5, 6).

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In contemporary classifications of mental disorders, such as the various editions of the APA's *Diagnostic and Statistical Manual of Mental Disorders,* the concept of "organic" has become more restricted, since there is no *overt* implication that the "nonorganic" disorders are functional or solely caused by psychological factors. The organic/nonorganic distinction is now used merely to separate mental (psychiatric) disorders that are due to an identifiable or presumed "physical" disorder (e.g., stroke, tumor) or to the effects of a psychoactive substance from mental disorders without such identifiable etiologies. These current nosologic distinctions have important prognostic and treatment implications, because they direct the clinician treating a patient with an organic mental disorder to pay special attention to the management (or detection, if the underlying disorder is unknown) of the underlying "physical" disorder or substance-induced condition.

We acknowledge the continued utility of identifying mental disorders caused by a "physical" disorder or substance abuse. The term "organic," however, is plagued by serious and, we believe, intractable connotative problems that have been noted previously (7). The connotative meaning of the term "organic" always returns to its historical roots, which imply a functional/structural, psychological/biological, and mind/body dualism that differs from the clinically useful nosologic distinctions we have just noted. These original dichotomies may have been valuable when we had little understanding of how the CNS functions, but they are at variance with the growing body of evidence of the importance of biological factors in the etiology of the major "nonorganic" mental disorders. Furthermore, the inevitable discomfort of labeling disorders such as schizophrenia and bipolar disorder as "nonorganic" leaves the clinician or researcher with no satisfactory alternative term for the antonym of "organic mental disorders." Finally, the organic/nonorganic distinction encourages the continued stigmatization of the mentally ill by suggesting that such "nonorganic" illnesses as schizophrenia and bipolar disorder are not true medical disorders. The term thus undermines recent efforts to educate the public as well as fellow physicians about our current understanding of mental disorders.

## THE PROPOSAL

As part of the development of *DSM-IV,* a proposal has been made for eliminating the term "organic" and for reorganizing the classification of the organic mental disorders (8). This proposal appears in the *DSM-IV Options Book* (9). In this proposal, disorders previously referred to as "organic mental disorders" would be renamed as either "secondary disorders," if they are due to medical disorders that are classified outside the mental disorders section of the *International Classification of Diseases (ICD)* (e.g., brain tumor, vascular disease, metabolic disturbance), or "substance-induced disorders" (e.g., cocaine intoxication delusional disorder).

In *DSM-III* and *DSM-III-R* the medical disorders classified outside the mental disorders section of the *ICD* were referred to, as is customary, as "physical disorders." Like the term "organic disorders," the term "physical disorders" has connotative problems. Thus, in the remainder of this article, and in *DSM-IV,* the precise if somewhat clumsy term "nonpsychiatric medical disorders" will be used. Thus, as already implicit in the *DSM-II, DSM-III,* and *DSM-III-R* classifications, all psychiatric (mental) disorders are conceptualized as a subset of the larger class of medical disorders.

One of the advantages of this proposal to eliminate the term "organic mental disorders" is that the disorders that previously were awkwardly referred to as "nonorganic" can now be called "primary mental disorders." This results in a clinically useful trichotomy that should facilitate communication about differential diagnosis, as in asking the question, Is this manic behavior *substance-induced, secondary* to a nonpsychiatric disorder, or *primary*?

In order to allow the clinician to indicate the specific etiology of a secondary disorder, the proposal instructs the clinician to include the name of the etiologic "physical" disorder, with both disorders coded on axis I. For example, what would be coded according to *DSM-III-R* as organic mood disorder on axis I and hypothyroidism on axis III would, according to this proposal, be coded as secondary mood disorder due to hypothyroidism on axis I (with a code number for each of the disorders).

One of the important organizing principles of *DSM-III* and *DSM-III-R* is the placement of disorders into major diagnostic groups that share phenomenologic features, so as to facilitate differential diagnosis. For example, in determining the diagnosis of a patient whose predominant symptoms involve a disturbance of mood, it is useful to group together disorders that, by definition, require a disturbance in mood. Therefore, in *DSM-III-R,* bipolar disorder, major depression, cyclothymia, and dysthymia are grouped together under the heading Mood Disorders. However, by having a separate class of organic mental disorders in *DSM-III* and *DSM-III-R,* disorders that are often critical in the differential diagnosis of the presenting disturbance are listed separately. Thus, organic mood disorder and substance-induced mood disorders are listed apart from the listing of the (primary) mood disorders. It is easy for the clinician looking at the *DSM-III* or *DSM-III-R* list of mood disorders to overlook the need to consider organic mood disorder and substance-induced mood disorders as well.

Another important aspect of the proposal addresses this problem by reorganizing the entire classification of mental disorders to distribute the secondary and substance-induced disorders into the major groups with which they share phenomenology. Each major group, such as the anxiety disorders, would begin with the primary disorders (e.g., panic disorder) followed by the secondary disorder (e.g., secondary anxiety disorder) followed by the substance-induced disorder (e.g., substance-induced anxiety disorder). The final category in each major group would be "not otherwise specified," to be used for those frequent instances in which the clinician (using our recommended terminology) is unable to make a judgment about whether the disturbance is secondary, substance-induced, or primary.

Following this principle for organizing major diagnostic groups on the basis of shared phenomenology, the proposal would group together delirium, dementia, and amnestic disorder under the rubric of "cognitive impairment disorders." This has the effect of listing all causes of these syndromes in the same section of the classification. This is in contrast to *DSM-III-R,* where, for example, the seven disorders associated with delirium are listed in three different sections of the classification (dementias arising in the senium and presenium, psychoactive substance-induced organic mental disorders, and organic disorders associated with axis III physical disorders).

Another way to facilitate differential diagnosis is to consider adding to the *DSM-IV* classification additional well-recognized drug-induced and secondary disorders that are not included in the *DSM-III-R* classification. Examples include drug-induced sexual disorders (e.g., cocaine-induced erectile dysfunction), secondary dissociative disorders (e.g., dissociative disorder due to epilepsy), and secondary catatonic disorder (e.g., catatonic disorder due to brain tumor).

## CRITICISMS OF THE PROPOSAL

There have been several criticisms of this proposal. Lipowski (10–12) has argued that the term "organic," properly defined, serves a useful function and that its abolition will create confusion, be at odds with *ICD-10,* and impede communication. Significantly, his definition of "organic" is in complete agreement with our definition of "secondary." Where we disagree is that we believe, as we have noted, that there is no way to avoid the incorrect connotations of the original historical meaning of the term "organic," which will always be a source of confusion when this term is used. The proposal for *DSM-IV* does deviate from *ICD-10* in both terminology and the organization of the classification. However, the constructs and codes of *DSM-IV* substance-induced and secondary disorders would be identical to the *ICD-10* constructs of substance-induced and organic mental disorders, ensuring that all cases would be classified in an equivalent way. Therefore, there should be no problem in ensuring compatibility between the two systems.

Several problems have been noted with the term "secondary." One problem is that the term has been used in psychiatry with a different meaning—to indicate that a mood disorder has temporally followed a nonmood disorder (13). However, this use of the term was primarily a research strategy for achieving maximum homogeneity in research samples and never received widespread clinical use. It has also been noted that intuitively, the term "secondary" should include disorders due to substance use. However, this leads to very cumbersome terminology when one is referring to disorders that are not primary but also not substance-induced; what we propose to call simply "secondary mood disorder" would have to be called something like "mood disorder due to a nonpsychiatric medical disorder." Another criticism is that the use of "secondary" in this context is imprecise, since, ultimately, one could argue that all disorders are secondary to some underlying process. However, applying the term "secondary" to all disorders would obscure what we have noted to be a useful treatment-relevant distinction within the classification of mental disorders. Finally, it has been argued that the term "secondary disorder" will be unfamiliar to nonpsychiatric physicians who are used to the term "organic." However, this objection overlooks the way in which the term will actually be used, as in "I think the problem is a secondary mood disorder due to hypothyroidism." When "secondary" is used in context, the nonpsychiatric physician will have no trouble understanding exactly what is meant by the term.

The term "secondary" became our final choice for the proposal only after we concluded that alternative terms were even less satisfactory. In our original proposal we had suggested the term "symptomatic," which had been used in this country with a similar meaning. The term even now has current usage in European psychiatry and is part of the chapter heading for the organic section of the mental disorders chapter of *ICD-10.* This term was ultimately rejected when we realized that in communications with our nonpsychiatric colleagues the term would be extremely confusing. (Consider the following exchange. Psychiatrist: "Thank you for referring Mr. Jones. I believe he suffers from a symptomatic mood disorder." Internist: "I don't understand what you are talking about. I know he is symptomatic—that's why I sent him to you.")

Because of the problems identified with finding a substitute for the term "organic," it has been suggested that the solution is to have no term at all, but merely to note, in the name of the disorder, the etiologic nonpsychiatric disorder, such as "depressive disorder due to hypothyroidism." However, in the absence of a generic term, such as "secondary depressive disorder," discussions of differential diagnosis would have to use very cumbersome language, for example, "Rule out a depressive disorder due to a nonpsychiatric medical disorder" (instead of simply "Rule out a secondary depressive disorder"). Furthermore, not having a generic term would preclude the availability of simple terminology for what we believe is a clinically useful conceptual trichotomy of all mental disorders as primary, secondary, or substance-induced.

Removing the term "organic mental disorders" from the classification may be viewed as radical. However, from another perspective these proposals for changes in terminology and reorganization of the entire classification are conservative, since they continue the traditional nosologic dichotomy between (to use the new terminology) primary mental disorders and those that are either substance-induced or secondary to a nonpsychiatric medical disorder. Fogel (14) has argued, using as an example the *DSM-III-R* distinction between major depression and organic mood disorder, that the reliability and validity of psychiatric diagnosis would be improved by keeping axis I strictly phenomenologic and identifying relevant organic factors on axis III. Organic factors judged to be causal or contributory to an axis I disorder could be indicated by a defined symbol, as discussed in Williams's 1985 review of critiques of the *DSM-III* multiaxial system (15, 16). Thus, Fogel argues that the current proposal would perpetuate what is now an unreliable and invalid nosologic distinction.

Fogel's suggestion of a purely descriptive axis I nosology may, at first glance, seem appealing. However, there are several problems with this suggestion. First, it is incompatible with the proposed *ICD-10* classification, which has largely adopted the *DSM-III-R* approach by including such categories as organic affective disorder, organic anxiety disorder, and organic personality disorder. Fogel's proposal would therefore significantly disrupt compatibility between *DSM-IV* and *ICD-10*. More important, if his proposal were systematically applied to other disorders, for example, schizophrenia, the same diagnostic term, perhaps "schizophrenic syndrome," would be applied to patients with schizophrenia-like symptoms regardless of whether drugs or nonpsychiatric medical disorders were judged to be the cause. Admittedly, the clinical judgment about the etiologic role of "organic" factors is often extremely difficult and sometimes impossible, but eliminating this treatment-relevant distinction from our nosology and relegating it to an axis III symbol hardly seems to represent an advance.

The term "cognitive impairment disorders" has been criticized on the grounds that cognitive impairment is frequently a prominent feature of other disorders, such as schizophrenia and major depression, and therefore it is misleading to single out delirium, dementia, and amnestic disorder as cognitive impairment disorders. However, cognitive impairment is, in fact, the defining feature of these three disorders, whereas it is not invariably present in any other mental disorders. (The exception to this is mental retardation, which by tradition, has always been classified outside the organic mental disorders.) In a similar fashion, mood disturbance is frequently a prominent feature of disorders that are not classified as mood disorders, such as schizophrenia, but it is the defining feature of all of the mood disorders.

The part of the proposal that would distribute the secondary and substance-induced disorders into the major diagnostic groups with which they share phenomenology has been criticized on two grounds. First, it is argued that if this is done, the unitary concept of "secondary" and "substance-induced" will be lost. Second, not having a single section for these disorders would make the classification less convenient for clinicians who focus primarily on the treatment of mental disorders in medical and substance abuse settings. We believe that these objections can be met by including appendices that list all of the secondary and all of the substance-induced disorders together.

## CONCLUSIONS

The organic/nonorganic distinction arose historically from the philosophical controversy about the relation between mind and brain, which continues to generate controversy in our field (17). The proposal we have outlined in no way solves this apparently intractable problem. However, we would argue that it provides a terminology that avoids a now outmoded conceptualization of the issues. Similarly, the historical distinction between psychiatric and nonpsychiatric disorders arose largely on the basis of practical considerations about which disorders were managed by which kinds of clinicians. While this distinction continues to have practical utility, the proposal does not help clarify the inherently difficult boundary between these two types of disorders or the related problem of defining mental (psychiatric) disorder itself (18).

Any change in terminology or the organization of the classification of mental disorders is a potential source of disruption for both researchers and clinicians. However, the potential benefits of this proposal for clarity and for facilitating differential diagnosis justify putting to rest the familiar but now anachronistic term "organic mental disorders."

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# Magnetic Resonance Imaging of the Posterior Fossa in Autistic Adults

**H. Jordan Garber, M.D., and Edward R. Ritvo, M.D.**

*Magnetic resonance imaging measurements were obtained for 12 adults with* DSM-III-*defined autism and a matched group of 12 normal subjects. No significant differences were found for mean midsagittal areas of pons, fourth ventricle, cerebellar vermis, or vermis lobules. No significant brain abnormalities were observed in either group.*

(Am J Psychiatry 1992; 149:245–247)

Although autistic disorder may result from organic insults (1) or genetic influences (2), brain imaging has not consistently shown structural abnormalities (3). Ventricular enlargement or reversed cortical asymmetry was noted in some autistic subjects by pneumoencephalography and CT but not by all investigators (4, 5), and various cortical abnormalities have been noted by magnetic resonance imaging (MRI) (6) but not in all studies (3). Evidence of abnormal CNS development in the posterior fossa has included 1) lower cerebellar Purkinje cell counts post-mortem (7, 8); 2) smaller midsagittal MRI area of the posterior-superior vermis (lobules VI and VII) in an autistic adult (9) and in 18 autistic subjects (mean age=20.9 years) compared with 12 normal subjects (10); and 3) smaller midsagittal MRI area of the pons (11) and larger fourth ventricle (12) in young autistic subjects (mean age=11.3 years) compared with normal subjects.

Our previous MRI study of 15 young autistic subjects (mean age=11.6 years) and 15 matched normal subjects found few structural abnormalities (3) and no significant differences for areas of the cerebellar vermis lobules (13), fourth ventricle (3), or pons (unpublished data). Because of possible maturational effects and age difference between our previous autistic subjects and those of Courchesne et al. (10), we used MRI to study adult autistic subjects.

## METHOD

The autistic adults were recruited through a university neuropsychiatric institute; they had been previously diagnosed according to *DSM-III* criteria by one of us (E.R.). The autistic subjects had middle to high functioning (14), were medication-free, and had no other medical or neurological illnesses. The normal comparison subjects, recruited by advertisement and personal contact, were of normal or higher intelligence and had no personal or family history of neurological or psychiatric illnesses. After approval from the Human Subjects Protection Committees at the university and after informed consent had been obtained from each subject or guardian, sagittal MRI was performed on 12 autistic subjects 18–38 years old (mean age=27.2 years, SD=5.3) and 12 normal volunteers 21–35 years old (mean age=26.4 years, SD=3.6). The groups did not differ by age ($t=0.407$, $df=22$, $p<0.69$) or sex distribution (three of the autistic subjects were women and nine were men; four of the normal subjects were women and eight were men).

Sagittal images were obtained at 1.5 T (Picker Vista MR, $T_1$-weighted sequence: repetition time=800 msec, time to echo=26 msec, two signals averaged, 256-gra-

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**TABLE 1. Measurements From Magnetic Resonance Imaging of 12 Adult Autistic Subjects and 12 Normal Subjects**

| | Autistic Subjects | | Normal Subjects | | Analysis | |
|---|---|---|---|---|---|---|
| Midsagittal Measurement | Mean | SD | Mean | SD | t (df=22) | p |
| Area | | | | | | |
| Cerebrum (cm$^2$) | 89.15 | 7.59 | 87.92 | 8.37 | 0.376 | <0.71 |
| Pons (cm$^2$) | 5.69 | 0.61 | 5.75 | 0.58 | 0.237 | <0.81 |
| Fourth ventricle (cm$^2$) | 1.10 | 0.22 | 0.96 | 0.22 | 1.697 | <0.10 |
| Cerebellar vermis | | | | | | |
| Total (cm$^2$) | 9.52 | 0.76 | 9.35 | 0.90 | 0.507 | <0.62 |
| Ratio of vermis to cerebrum | 0.11 | 0.01 | 0.11 | 0.02 | 0.024 | <0.98 |
| Lobules I–V (cm$^2$) | 4.63 | 0.51 | 4.48 | 0.40 | 0.803 | <0.43 |
| Lobules VI–VII (cm$^2$) | 3.15 | 0.43 | 2.99 | 0.41 | 0.969 | <0.34 |
| Ratio of lobules VI–VII to I–V | 0.69 | 0.14 | 0.67 | 0.08 | 0.527 | <0.60 |
| Volume of fourth ventricle (cm$^3$) | 1.11 | 0.15 | 0.99 | 0.20 | 1.670 | <0.11 |

dient steps, interleaved multislice technique, 12 contiguous slices, 5-mm thick). Midsagittal slices were positioned in a standardized manner from the coronal pilot scan of each subject as described elsewhere (3); the sagittal image grid was centered on the third ventricle and apex of the fourth ventricle. Results were evaluated by two MRI radiologists who were blind to diagnosis.

Areas were measured by two independent and blind raters using computerized planimetry functions of the MRI console (magnified four times, consistent windows and levels). Pontine boundaries were defined as described by Gaffney et al. (11); fourth ventricle measurements were made as we reported elsewhere in detail (3); boundaries within the cerebellar vermis were defined as described by Courchesne et al. (10). Total vermis area measurement used a caudal boundary defined by a line joining the apex of the fourth ventricle to the posterolateral fissure, to include lobules VIII (pyramis) and IX (uvula) but to exclude nodulus. Total cerebral area was measured on the midsagittal slice.

Measurements were made twice by each rater, and the four values were averaged. Values had intraclass correlations greater than 0.92 (intrarater) and greater than 0.91 (interrater) for all measures. Student's t tests (two-tailed) were used for between-group comparisons, and Pearson correlation coefficients were used to explore within-group relationships of measurements with age.

## RESULTS

Radiologic evaluation of all sagittal images revealed no significant focal abnormalities in either the autistic group or the normal comparison group. Enlargement of the lateral ventricles was noted in one autistic subject and one normal subject, but no abnormalities were apparent in the posterior fossa of any of our subjects.

Results of morphologic measurements are given in table 1. There were no differences between groups for midsagittal measures of the pons, fourth ventricle, vermis, or vermis lobules. Area ratios of total vermis to cerebrum and of lobules VI–VII to lobules I–V did not differ between groups. Correlations of age were significant only for increasing age with greater pontine area ($r=0.60$, $N=12$, $p<0.04$) and fourth ventricle volume ($r=0.62$, $N=12$, $p<0.03$) in normal subjects but not in autistic subjects (pons: $r=0.18$, $N=12$, $p<0.58$; fourth ventricle volume: $r=0.18$, $N=12$, $p<0.58$). Between-group differences for age correlations were not statistically significant.

## DISCUSSION

Consistent with our previous study of younger autistic subjects (3, 13), we found no focal abnormalities and no measurable differences in the posterior fossa of autistic adults compared with normal subjects. Although Courchesne et al. (9, 10) noted vermal hypoplasia as a significant finding in some autistic subjects, we have not observed this in any autistic subject. However, we excluded autistic subjects with low functioning or any "organic history," and radiologic evaluations were limited to sagittal images. Since Gaffney and Tsai (6) noted MRI abnormalities in six of 14 autistic subjects, three of whom had substantial medical histories or evidence of neurological disease, MRI may be revealing when there is a high index of suspicion for specific CNS abnormalities. Nonetheless, our results do not confirm previous findings of abnormal pontine (11), cerebellar (10), or fourth ventricle (12) areas in autistic disorder.

We incorporated several methodological improvements in this study: 1) our comparison group was selected specifically as normal subjects for autism research (previous investigators used "radiologic control" cases from MRI files [10–12]); 2) we used one MRI protocol with consistent midsagittal slice positioning (Courchesne et al. [10] and Gaffney et al. [6, 11, 12] used varying MRI methods within groups, and neither defined the midsagittal position); and 3) we obtained contiguous 5-mm thick slices (Gaffney et al. [6, 11, 12] used 1-cm thick slices and Courchesne et al. [10] left gaps between slices, both of which may have affected accuracy). Our measurements had high reproducibility and reliability, yielding a normal ratio for vermis to cerebrum similar to previously reported values of 0.09 (16) and 0.11 (3).

We found significant age correlations with pontine area and fourth ventricle volume in normal subjects but not in autistic adults. Gaffney et al. (11) also found that age correlated with pontine area in normal subjects and not in autistic subjects but did not evaluate age effects on the fourth ventricle (12). Although the difference in correlations between our groups was not statistically significant, the small size of these groups may have obscured differences by type II errors. Larger groups and longitudinal studies are needed to further evaluate maturational effects on the posterior fossa in autism.

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# High-Intensity Signals in Alzheimer's Disease Without Cerebrovascular Risk Factors: A Magnetic Resonance Imaging Evaluation

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*The authors examined the relationship between Alzheimer's disease, without cerebrovascular risk factors, and high-intensity signals on magnetic resonance imaging (MRI) with a 1.5-tesla scanner. There were no significant differences in MRI high-intensity signals between subjects with Alzheimer's disease (N=16) and healthy control subjects (N=23).*

(Am J Psychiatry 1992; 149:248–250)

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Alzheimer's disease is the most common cause of dementia in the Western hemisphere, and several technologically advanced imaging modalities including magnetic resonance imaging (MRI) have been used to study Alzheimer's disease (1, 2). The unprecedented sensitivity of MRI to brain pathology and its increasing use have led to a plethora of reports purporting to show structural abnormalities across a broad spectrum of neuropsychiatric conditions including Alzheimer's disease (3, 4).

High-intensity signal abnormalities on MRI—regions that appear bright on $T_2$-weighted and proton density images—have received considerable attention (1, 3). They are located primarily in the periventricular white matter, deep white matter, and subcortical regions of the brain. While the precise etiology of these signals remains unclear, it appears likely that several factors including ischemic changes, increased water content of brain tissue, and demyelination may be responsible for their presence (3). They have been reported in several conditions including normal aging, multiple sclerosis, hydrocephalus, multi-infarct dementia, and affective disorders (3, 4). There are conflicting reports regarding the presence of MRI high-intensity signals in Alzheimer's disease and the role of associated vascular risk factors in their development (1, 2, 5).

This study was designed to clarify the relationship between periventricular and deep white matter high-intensity MRI signals and Alzheimer's disease unassociated with major cerebrovascular risk factors. In addition, we sought to examine certain subcortical gray nuclei—caudate, lenticular nuclei, and thalamus—in Alzheimer's disease for the presence of high-intensity signals and to compare these to signal changes in healthy, age-matched control subjects.

## METHOD

The study groups consisted of 16 subjects with probable Alzheimer's disease (eight women, eight men; mean age=67 years, SD=8) and 23 healthy, age-matched control subjects (12 women, 11 men; mean age=68 years, SD=8). The Alzheimer's disease subjects met the criteria for probable Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (6) and were free of major vascular risk factors such as hypertension, strokes, transient ischemic attacks, and diabetes. All Alzheimer's disease subjects, with the exception of two, had Mini-Mental State examination scores (7) greater than 16 (mean=23, SD=5). Two Alzheimer's disease subjects had Mini-Mental State examination scores of 12 each. The control subjects were screened according to the same health criteria as the Alzheimer's disease subjects and were also free of significant neurological, psychiatric, and systemic disease; head injury; and major vascular risk factors such as hypertension, transient ischemic attacks, and diabetes. In addition, both Alzheimer's disease and control subjects had normal laboratory indices, i.e., complete and differential blood counts; he-

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patic, renal, and thyroid panels; $B_{12}$ and folate levels; and syphilis serology.

The MRI studies were performed with a 1.5-tesla General Electric Signa scanner (Milwaukee, Wis.) and with a quadrature head coil. Scans included sagittal short repetition time and axial long repetition time series with 5-mm contiguous slices. Only the transaxial $T_2$-weighted and proton density images (repetition time=3000 msec, echo times=30 and 80 msec) were examined by a qualified neuroradiologist (D.Y.) for evaluation of periventricular white matter high-intensity signals, deep white matter high-intensity signals, and subcortical gray nuclei high-intensity signals. The neuroradiologist was blind to the clinical status of all subjects.

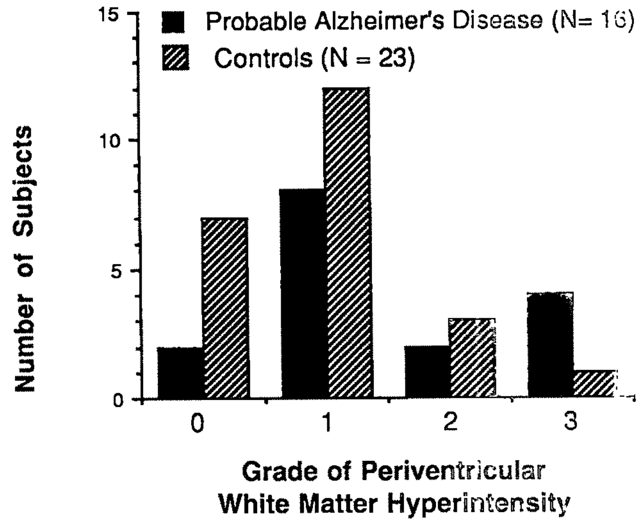
Periventricular high-intensity signals were rated by the neuroradiologist on a 0–3 scale of severity (1) (0=absent, 1=frontal or occipital caps or pencil-thin lining of the lateral ventricle, 2=smooth halo around the lateral ventricle, 3=irregular periventricular high-intensity signals extending into the deep white matter). Deep white matter high intensities were also graded on a scale of 0–3 (1) (0=absent, 1=punctate foci, 2=early confluence of foci, 3=large confluence of foci). High-intensity signals in the caudate and lenticular nuclei and thalami were rated as follows: 0=absent, 1=punctate, 2=multipunctate, 3=diffuse (4).

The robust rank-order test was used to examine differences in ratings between the Alzheimer's disease and control groups in periventricular white matter high-intensity signals, deep white matter high-intensity signals, and subcortical gray nuclei high-intensity signals. Within both groups the Spearman rank-order correlation coefficient was used to determine whether there was any association among serum cholesterol and triglyceride levels, Mini-Mental State examination scores; age; and ratings of periventricular, deep white matter, and subcortical high-intensity signals.

## RESULTS

In our study groups, 37% (N=6) of the Alzheimer's disease subjects and 17% (N=4) of the control subjects had periventricular white matter high intensity of grade 2 or greater. The exact number of Alzheimer's disease and control subjects who fell into specific periventricular white matter high-intensity severity groups is displayed in figure 1. Nineteen percent (N=3) of Alzheimer's disease subjects and 9% (N=2) of control subjects presented with deep white matter high intensity of grade 2 or greater. Regarding subcortical high-intensity signals, none of the Alzheimer's disease subjects and 9% of the control subjects had subcortical gray nuclei high-intensity signal changes of grade 2 or greater. The differences between the Alzheimer's disease and control groups on all three measures were statistically insignificant (robust rank-order test). Using the Spearman rank-order correlation test (after correcting for ties), we found that within the Alzheimer's disease group there were positive correlations between age and both periventricular white matter high intensity ($r_s$=0.5, df=14, $p<0.01$) and deep white matter high intensity ($r_s$=0.55, df=14, $p<0.01$) and between subcortical gray nuclei and Mini-Mental State examination scores ($r_s$=0.59, df=14, $p<0.01$). The control group demonstrated a significant inverse correlation between serum triglyceride levels and subcortical gray nuclei high-intensity signals ($r_s$=−0.46, df=21, $p<0.05$).

**FIGURE 1. Severity of Periventricular White Matter High-Intensity Signals in Subjects With Probable Alzheimer's Disease and Healthy Control Subjects**



## DISCUSSION

These data demonstrate that in our study groups, in the absence of major vascular risk factors such as hypertension, diabetes, and cerebral ischemic events, the Alzheimer's disease group was not associated with a statistically significant higher prevalence of high-intensity signals than was the healthy, age-matched control group. Compared with the control group, the Alzheimer's disease group did, however, have twice the prevalence of periventricular high-intensity signals. In addition, within the Alzheimer's disease group both periventricular white matter high intensity and deep white matter high intensity increased significantly with age, while subcortical gray nuclei high-intensity signals showed a significant inverse correlation with severity of dementia, as measured by the Mini-Mental State examination. The prevalence of MRI high-intensity signals in the healthy elderly control group was low and consistent with other reports that demonstrated a low prevalence of high-intensity signals in healthy subjects (5). The inverse correlations between subcortical gray nuclei and triglyceride levels in control subjects and between subcortical gray nuclei high-intensity signals and clinical severity in Alzheimer's disease subjects are counterintuitive and do not have any obvious explanation.

MRI high-intensity signals have been reported across a broad spectrum of clinical conditions (3, 4). While there are conflicting reports regarding the presence of high-intensity signals in Alzheimer's disease (1, 5, 8), several fundamental clinical and methodological factors may explain the apparent discrepancies among studies. Earlier reports demonstrating a higher prevalence of periventricular white matter high-intensity signals in Alzheimer's disease combined subjects with probable/possible Alzheimer's disease in their samples or combined Alzheimer's disease subjects and subjects with vascular dementia (1, 2, 8). In addition, the probable Alzheimer's disease group included subjects with essential hypertension—a major cerebrovascular risk factor that has consistently been shown to be associated with MRI high-intensity signals (1, 9). It should be pointed out that the presence of hypertension per se does not preclude a diagnosis of probable Alzheimer's disease based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (6). However, in order to determine whether high-intensity signals on MRI are associated with the pathophysiology of Alzheimer's disease, it is necessary to restrict the study sample to carefully screened Alzheimer's disease subjects who are free of confounding risk factors.

Our finding of a low prevalence of MRI high-intensity signals in a healthy elderly control group that was free of significant vascular risk factors corroborates earlier reports on MRI high-intensity signals in healthy elderly subjects (5, 9). In elderly subjects the presence of MRI high-intensity signals correlates significantly with age and vascular risk factors, especially hypertension and cerebral ischemia (9). The prevalence of high-intensity signals has also been shown to be high in subjects with stroke and vascular dementia (5, 10). Collectively, these findings indicate that overt and subclinical vascular disease is largely responsible for the signals often observed in the elderly.

The pathophysiological factors responsible for high-intensity signals may vary across clinical conditions. In healthy elderly subjects the low myelin content of axons around the frontal horns, loss of ventricular ependymal lining, and the convergence of interstitial fluid to the frontal horns may contribute significantly to the signals on MRI (3). Ischemic changes, the dilation of perivascular spaces, and vascular ectasia are considered responsible for the signals in vascular dementia and strokes (10). In multiple sclerosis, subependymal demyelination is believed to be the explanation for the signals seen (3). Thus there is compelling evidence to suggest that high-intensity signals are nonspecific in etiology and that a variety of pathophysiological mechanisms, both vascular and otherwise, can produce the same appearance on MRI.

These data establish that in our study group of probable Alzheimer's disease subjects who were free of major vascular risk factors, the prevalence of MRI high-intensity signals was low and not significantly different from that of healthy control subjects. The prevalence of periventricular white matter high-intensity signals was greater, albeit statistically insignificant, in the Alzheimer's disease group than in the control group. It is possible that the relatively small size of our study groups precludes the higher prevalence of periventricular white matter high intensity in the Alzheimer's disease group from becoming statistically significant. In addition, our current study group was restricted to subjects with mild to moderate dementia. It is therefore possible that severe Alzheimer's disease may be associated with a higher prevalence of high-intensity signals on MRI. Future studies aimed at further clarification of this question should extend the study to well-characterized Alzheimer's disease subjects with severe cognitive impairment. Special attention should continue to be paid to screening out confounding conditions and risk factors that limit interpretation of data.

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# Glutamate and Other CSF Amino Acids in Alzheimer's Disease

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*The authors compared CSF amino acid levels of 10 patients with mild to moderate dementia and probable Alzheimer's disease who had never received antidepressant or neuroleptic medication with those of 10 normal subjects of similar age. The Alzheimer's patients had significantly higher levels of CSF glutamate. This finding was not related to age, sex, or severity of dementia. Elevated CSF glutamate may reflect greater glutamatergic activity early in the course of Alzheimer's disease. The authors speculate that the excitotoxic effects of glutamate may contribute to progressive neuronal loss in Alzheimer's disease.*

(Am J Psychiatry 1992; 149:251–254)

Numerous neurotransmitters, including acetylcholine, norepinephrine, serotonin, somatostatin, and corticotropin-releasing factor (CRF), have been clearly implicated in Alzheimer's disease, but there is a growing body of evidence suggesting that excitatory amino acids, particularly glutamate, may also have an important role in this disease. Excitatory amino acid neurotransmitters such as glutamate and aspartate are known to have neurotoxic (excitotoxic) effects that have been implicated in stroke, head trauma, and seizure disorders. More recently, there has been considerable interest in excitatory amino acid theories of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (1).

Animal experiments have suggested that excitatory amino acid neurotransmitter systems—specifically the N-methyl-D-aspartate (NMDA) receptor, a type of glutamate receptor—are important in learning and memory. As reviewed by Greenamyre and Young (2), NMDA antagonists have been shown to prevent spatial discrimination learning. Furthermore, it has been hypothesized that NMDA receptor stimulation may be necessary for new learning. Given the possible role of excitatory amino acid neurotransmitter systems in memory and learning as well as reports of lower levels of brain glutamate levels (3–5) and less glutamate receptor density (especially the NMDA receptor) (6–8) in Alzheimer's disease, it is reasonable to hypothesize that alterations in glutamatergic activity may play a role in both the clinical features and the pathophysiology of Alzheimer's disease (2, 9). Koh et al. (10) have recently found that beta-amyloid, a protein that is widely present in the brain of subjects with Alzheimer's disease, can increase susceptibility to excitotoxic agents such as glutamate.

Several post-mortem studies have compared brain glutamate levels in Alzheimer's disease to those in control subjects. Although Tarbit et al. (11) reported no difference in the hippocampus, other investigators (3–5) have found lower levels of glutamate in the frontal cortex and the temporal cortex of Alzheimer's patients than in control subjects. These findings of lower glutamate concentrations in the cortexes of presumably severely impaired patients with Alzheimer's disease are consistent with a decrease in glutamatergic activity in end-stage Alzheimer's disease.

Glutamate has also been studied in vivo in Alzheimer's disease. Procter et al. (4) measured antemortem levels in biopsy specimens and found that glutamate was significantly reduced in the temporal cortex but not in the frontal cortex of patients with Alzheimer's disease. The reduction in glutamate in the temporal cortex of these antemortem biopsy specimens was smaller than that found in a post-mortem sample, which presumably represented later stages of Alzheimer's disease (4). This may suggest that decreasing brain glutamate levels parallel disease progression.

Studies of CSF provide another method of examining progressively degenerative diseases such as Alzheimer's during early stages. In an attempt to evaluate possible alterations in excitatory amino acids before the end stage of the illness, several investigators have examined excitatory amino acids in the CSF of patients with Alzheimer's disease. Three CSF studies found no significant difference between patients with Alzheimer's disease and control subjects (4, 12, 13). Unfortunately, these studies had one or more methodological limita-

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**TABLE 1. Concentrations of Free Amino Acids in CSF of Normal Comparison Subjects and Patients With Alzheimer's Disease**

| | Concentration (nmol/ml) | | | | | |
|---|---|---|---|---|---|---|
| | Comparison Subjects (N=10) | | Patients With Alzheimer's Disease (N=10) | | Analysis | |
| Amino Acid | Mean | SD | Mean | SD | t (df=18) | p |
| Higher in patients with Alzheimer's disease | | | | | | |
| Glutamate | 5.6 | 0.7 | 7.4 | 1.5 | 3.49 | 0.004 |
| Proline[a] | 2.2 | 0.5 | 3.0 | 1.0 | 2.26 | 0.04 |
| Lower in patients with Alzheimer's disease | | | | | | |
| Taurine[b] | 3.9 | 0.9 | 2.5 | 0.9 | 3.18 | 0.006 |
| Ornithine[b] | 5.2 | 1.2 | 3.0 | 2.3 | 2.68 | 0.02 |
| Lysine[b] | 30.8 | 2.6 | 18.6 | 7.6 | 2.51 | 0.03 |
| Same in both groups | | | | | | |
| Glutamine | 566.2 | 45.3 | 596.5 | 66.5 | 1.19 | 0.25 |
| Aspartate | 0.5 | 0.2 | 0.7 | 0.3 | 1.76 | 0.09 |
| Threonine | 28.7 | 8.5 | 35.6 | 7.9 | 1.84 | 0.08 |
| Glycine | 8.0 | 2.1 | 9.5 | 4.5 | 0.67 | 0.51 |
| Alanine | 34.3 | 13.3 | 33.7 | 7.7 | 0.11 | 0.91 |
| Tyrosine | 10.3 | 1.9 | 11.1 | 1.8 | 0.92 | 0.37 |
| Serine | 26.7 | 3.5 | 28.0 | 3.6 | 0.85 | 0.41 |
| Asparagine | 6.9 | 2.0 | 6.9 | 0.9 | 0.01 | 0.99 |
| Histidine | 8.5 | 3.5 | 12.7 | 5.9 | 1.92 | 0.08 |
| Arginine | 20.8 | 2.7 | 21.3 | 2.9 | 0.39 | 0.70 |
| Valine | 11.1 | 1.7 | 14.6 | 7.0 | 1.53 | 0.15 |
| Methionine | 3.5 | 0.7 | 3.8 | 0.7 | 0.89 | 0.39 |
| Isoleucine | 5.8 | 2.0 | 6.4 | 1.7 | 0.75 | 0.46 |
| Leucine | 14.9 | 4.9 | 15.6 | 3.3 | 0.34 | 0.74 |
| Phenylalanine | 8.7 | 1.6 | 9.7 | 1.5 | 1.37 | 0.19 |

[a] Values for only eight patients with Alzheimer's disease were available; df=16.
[b] Values for only nine patients with Alzheimer's disease were available; df=17.

tions, including 1) use of patients with a history of receiving psychotropic medication, 2) use of young control subjects or control subjects with other neurological disorders, and 3) inclusion of subjects with Alzheimer's disease whose degree of dementia was not specified. In the current study, we measured CSF concentrations of free glutamate and other amino acids in patients with probable Alzheimer's disease who had mild to moderate dementia and who had never received psychotropic drugs. These CSF amino acid levels were compared to those of subjects of similar age.

## METHOD

The 10 subjects with dementia—four men and six women—had a mean age of 59.7 years (SD=10.8) and met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders criteria for probable Alzheimer's disease as well as the *DSM-III* criteria for primary degenerative dementia. These patients were compared with 10 subjects—four men and six women—of similar age; their mean age was 63.8 years (SD=11.2). Patients were mildly to moderately demented (mean Global Deterioration Scale [14] score=4.7, SD=0.4; mean WAIS-R [15] score=79.4, SD=10.9; mean Mini-Mental State examination [16] score=16.6, SD=3.9) and were being cared for by their families at home. The mean duration of illness as reported by caregivers was 5.4 years (SD=4.7). Comparison subjects were free of medical and psychiatric illness. None of the participants had a history of treatment with neuroleptics or antidepressants. All patients and comparison subjects consented to participation in the study after its nature had been explained to them.

Lumbar punctures were performed with patients in the lateral decubitus position between 8:00 and 9:00 a.m. following overnight bed rest and fasting. Approximately 20 cc of CSF was collected on ice in a standardized manner and immediately frozen at –70 °C. Aliquots from a pooled specimen of the 3rd–17th ml were used for determination of free amino acids by using precolumn derivatization with 1-naphthylisocyanate and separation with reverse high performance liquid chromatography on a C18 silica column (17).

## RESULTS

As shown in table 1, the mean CSF concentration of free glutamate was significantly higher in patients with Alzheimer's disease than in comparison subjects. The mean CSF proline level of the patients was also significantly higher than that of the comparison subjects. Although the mean CSF aspartate level was not significantly higher in patients with Alzheimer's disease, CSF aspartate correlated strongly with glutamate ($r=0.83$, $N=10$, $p<0.001$). In contrast to findings of higher levels of glutamate and proline, patients with Alzheimer's disease had lower mean CSF concentrations of taurine, ornithine, and lysine than the comparison group.

Pearson correlations revealed no significant relationship between glutamate concentrations and severity of dementia as measured by the Global Deterioration Scale and the Mini-Mental State examination. However, it should be noted that the range of severity in our patients was somewhat constricted in that all patients had a Global Deterioration Scale score of 4 or 5. No significant relationships were found between CSF glutamate concentration and age, gender, or duration of illness.

## DISCUSSION

Excitatory amino acids in general and glutamate in particular have been hypothesized to contribute to a neurotoxic process involved in the pathogenesis of Alzheimer's disease (9). Although not consistently found in all reports, glutamate and its receptors have been observed to be lower than normal in post-mortem studies of patients with Alzheimer's disease. Although previous CSF studies have not demonstrated a difference in CSF glutamate levels between subjects with Alzheimer's disease and control subjects (4, 12, 13), Smith et al. (12) did find a significant positive correlation between CSF glutamate levels (which were not different from those of control subjects) and cognitive impairment in Alzheimer's disease.

There are methodological limitations, however, to the existing CSF studies. These include use of control subjects with neurological disorders (4, 12), use of young or not age-matched control subjects (12, 13), and failure to specify drug status or maintain all subjects drug free (4, 13). Procter et al. (4) and Smith et al. (12) used patients with neurological disorders as control subjects, and these disorders themselves could affect CSF levels of glutamate or other amino acids. The subjects with Alzheimer's disease in the reports by Procter et al. (4) and Degrell et al. (13) were not all kept drug free. This is an important shortcoming because neuroleptics antagonize the effects of dopamine, which is known to modulate glutamate release (18). The effects of neuroleptics on CSF glutamate levels may have masked any differences between groups. Although Smith et al. (12) did keep their subjects with Alzheimer's disease drug free for 1 week, this is a relatively brief period for complete washout of neuroleptic effects.

The precise relationship between glutamate and the severity of Alzheimer's disease remains unclear. Although most studies reported lower brain glutamate levels, the subjects in these reports were generally in the later stages of the disease. Unfortunately, Smith et al. (12) and Procter et al. (4) did not report the severity or duration of illness in their subjects with Alzheimer's disease in adequate detail. However, Degrell et al. (13) found a trend ($p<0.10$) for CSF glutamate levels to be negatively associated with age in a group of senile subjects with Alzheimer's disease. To the extent that severity of Alzheimer's disease parallels increasing age, this supports a theory of progressive loss of glutamatergic activity in Alzheimer's disease and is consistent with the glutamate hypothesis of Alzheimer's disease proposed by Maragos et al. (9). Unfortunately, the finding of Smith et al. (12) that CSF glutamate in Alzheimer's disease (although not different from control subjects) positively correlated with cognitive impairment is difficult to integrate into this model without more information about severity and duration of illness in those subjects.

Our data are consistent with the glutamate hypothesis of Alzheimer's disease, which suggests that glutamatergic activity is greater in the early stages of the disease. However, a more intriguing question, as yet unanswered, is whether there are glutamatergic abnormalities that precede the onset of clinical symptoms of dementia and that might, in fact, lead to Alzheimer's disease. Although perhaps methodologically difficult, it would be important to study glutamate in a group of normal elderly subjects and follow them longitudinally as some of them developed Alzheimer's disease. This would allow direct exploration of whether glutamate activity is higher in the very early stages of Alzheimer's disease.

It is important to note the limitations of this pilot study. The elevation in glutamate levels was slight and may have been due in part to conversion of glutamine to glutamate during storage of the CSF samples. However, this effect should have occurred in CSF samples from both comparison subjects and patients because samples from both groups were handled identically. Another limitation is the interpretation of changes in CSF glutamate levels as reflecting changes in transmitter glutamate. In fact, only a small portion of brain glutamate is in the transmitter pool, while the majority of brain glutamate is used intracellularly for metabolic processes. CSF glutamate may also originate in the spinal cord. The actual percentage of CSF glutamate that arises from the transmitter pool is unknown and may be small.

In addition to higher glutamate levels, we also observed that CSF taurine levels were lower in Alzheimer's disease. Since taurine is thought to be an inhibitory neuromodulator, lower taurine levels might reflect decreased inhibitory tone, which might facilitate greater glutamatergic activity. We also found that CSF proline levels were higher in patients than in comparison subjects. Although proline, like taurine, is thought to have inhibitory effects, it might also affect glutamate levels because it is a potential substrate for glutamate synthesis (19). Furthermore, proline itself is believed to modulate the NMDA receptor. Levels of ornithine, another potential substrate for glutamate synthesis (19), were also lower in patients than in comparison subjects. The significance of lower CSF lysine levels is unknown.

We were unable to correlate CSF glutamate levels with severity of dementia. However, our study group was small and represented a narrow range of impairment. Without a larger study group demonstrating a wider range of impairment, we cannot adequately test whether glutamate levels decrease as Alzheimer's disease progresses, as suggested by Degrell et al. (13).

To the extent that CSF glutamate levels reflect glutamate neurotransmitter activity, our findings may be due to greater glutamate activity in early Alzheimer's disease and provide support for the glutamate hypothesis of Maragos et al. (9), who stated, "Cell death due to neuronal toxicity could result from excessive synthesis or release of glutamate or a glutamate-like substance, faulty glutamate reuptake, decreased glutamate degradation, or decreased inhibition of excitatory neurons. Any of these aberrant processes could, early in the disease, increase local levels of glutamate and so initiate a slow, progressive degeneration and eventual death of neurons." Our data, derived from a small group of mildly to moderately demented subjects, are consistent with this hypothesis.

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# Modified Activity of the Human Auditory Cortex During Auditory Hallucinations

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*Previous reports have shown abnormalities in brain metabolism and evoked responses of schizophrenic patients with hallucinations. The authors recorded electric and magnetic auditory responses during transitory auditory hallucinations in two patients. Small but replicable response delays occurred during hallucinations. The results suggest that the effect of hallucinations on auditory cortex activity is similar to the effect of real sounds.*

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Auditory hallucinations are one of the main symptoms that characterize the acute phase of schizophrenia. In positron emission tomography and single photon emission tomography studies, hallucinations have been associated with increased glucose metabolism in the right hemisphere (1), especially in the hippocampus, parahippocampus, and amygdala (2). Therefore, hallucinations may result from hyperactivity in the limbic area resulting from a lack of normal neocortical inhibition (2). Patients suffering from chronic auditory hallucinations tend to show greater than normal glucose metabolism in the left temporal area (3). Abnormalities in auditory evoked potentials have been observed at the brainstem level (4).

Magnetoencephalography (MEG) is a relatively new noninvasive method based on the detection of cerebral magnetic fields outside the skull (5). Whereas the EEG results from neural currents oriented both radially and tangentially to the skull, MEG is sensitive to tangential currents only, thus mainly reflecting activity of pyramidal cells in the fissural cortex. Magnetic fields are not substantially affected by layers of inhomogeneous electric conductivity, as are the skull and the scalp. Therefore, with MEG it is possible to study cortical brain activity with good spatial and temporal resolution.

Continuous speech and music maskers delivered to one ear dampen and delay the N100m response (magnetic deflection peaking around 100 msec) to stimuli of both ears (6). In the present study we recorded auditory evoked potentials and auditory evoked magnetic fields during hallucinations and normal periods in two patients in order to detect signs of an analogous "internal masking."

## METHOD

### *Subjects*

We studied two cooperative male patients suffering from intense transitory hallucinations. Subject 1 (35 years old) had committed several thefts and robberies but had been found not responsible for his actions for reasons of insanity caused by schizophrenia. Subject 2 (44 years old) fulfilled the *DSM-III-R* criteria for schizophrenia. Both patients had their eyes open during the recordings and indicated with finger movements the beginnings and endings of auditory hallucinations. Long-latency auditory evoked potentials were recorded for subject 1, and auditory evoked magnetic fields were recorded for subject 2.

### *Recordings and Data Analysis*

In the recordings of auditory evoked potentials (subject 1), the stimuli were binaural 50-msec, 800-Hz sine wave tones, 60 dB above the hearing level, delivered once every second. Responses were measured from EEG derivations vertex—left mastoid and vertex—right mastoid. Recordings were carried out during two periods of hallucinations and two normal periods, and 75 responses were averaged each time. The first response during each recording period was omitted.

Recording of the auditory evoked magnetic fields

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(subject 2) was carried out in a magnetically shielded room; another person was with the patient inside the room. The stimuli were 1000-Hz, 80-dB, 50-msec square wave tones, administered to the subject with a plastic tube once every 0.9 seconds. The magnetic field over the right hemisphere was measured with a first-order SQUID (superconducting quantum interference device) magnetometer (figure 1). The initial recordings were made with a 7-channel axial gradiometer (7), and the second set of measurements was made with a 24-channel gradiometer (8). The 24-channel device has planar flux transformers: two orthogonal figure-of-eight flux transformers measure the derivatives $\partial B_r/\partial x$ and $\partial B_r/\partial y$ of the radial magnetic field component $B_r$ simultaneously at 12 locations, 3 cm apart from each other (figure 1). The planar gradiometer records the largest signal just above the active brain area.

The sensors' exact locations and orientations with respect to the head were determined by recording the magnetic field produced by small coils fixed on the scalp (7). Response amplitudes were measured relative to a 50-msec prestimulus baseline. The equivalent sources were found (by using the simultaneously recorded 24 signals) by a least-squares fit in a spherical volume conductor, adjusted to the local radius of curvature of the head in the measurement area. The first two responses in each recording period were omitted.

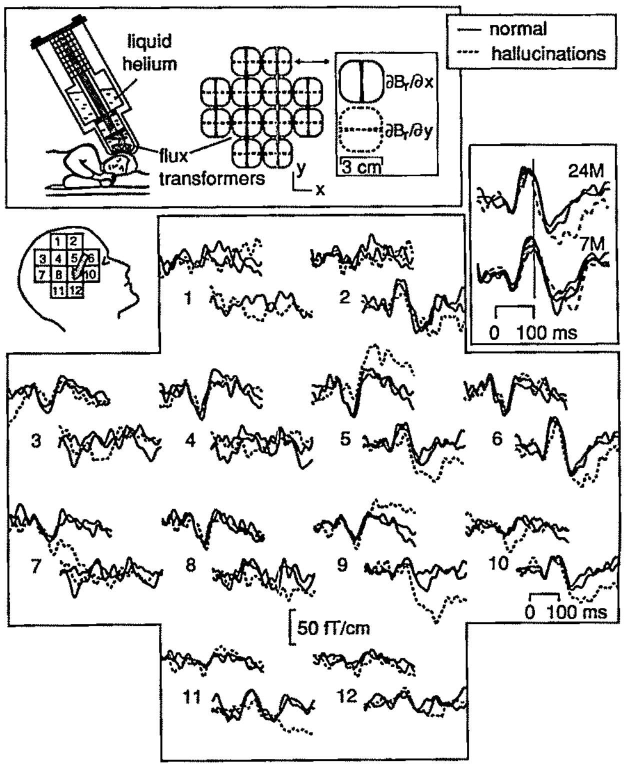
## RESULTS

Auditory evoked potentials were recorded from subject 1 during two hallucination and two normal periods. The main response (N100) peaked at 80 msec during the normal periods but was delayed by about 20 msec during hallucinations. The amplitudes of N100 were not affected, but the late positive potentials over the right hemisphere were slightly increased during hallucinations.

Figure 1 shows the auditory evoked magnetic fields of subject 2 over the right hemisphere, recorded with the 24-channel gradiometer. During the normal periods there were typical auditory responses and a prominent N100m, peaking at 73–94 msec depending on the channel. During hallucinations N100m was narrower; it peaked at 92–98 msec and was dampened in several channels. Further, a late deflection of opposite polarity was seen around 200 msec with a distribution different from that of N100m. Since hallucinations occurred during only one recording period, data are also shown from the earlier 7-channel measurements, in which hallucinations occurred during one recording out of four (the second one). During the normal periods N100m peaked at 80–89 msec, and during hallucinations it peaked at 101 msec. On average, N100m was slightly smaller during hallucinations. The results of these two studies were thus very similar.

The equivalent dipole for N100m explained 90% of the field variance during the normal period (see figure 1, head). The source location is similar to that observed in healthy subjects and suggests activation of the supratemporal auditory cortex (9). During hallucinations the source of N100m was within 1 cm of this site, but the dipole model explained only 73% of the variance.

**FIGURE 1. Auditory Evoked Magnetic Fields Over the Right Hemisphere in a Schizophrenic Subject During Hallucinations and Normal Periods[a]**



[a] The top section represents the experimental arrangement for recording magnetic brain signals. The subject is lying in a magnetically shielded room, and the magnetometer, which has sensors immersed in liquid helium, is placed close to the subject's head. For a description of the flux transformer array, see text. The main figure shows auditory evoked magnetic fields recorded with a 24-channel gradiometer during two normal periods and one period of hallucinations. The passband is 0.05–40 Hz. The recording locations are shown on the schematic head. The upper trace of each pair indicates the field gradient in the vertical direction ($\partial B_r/\partial y$), and the lower shows the field gradient in the horizontal direction ($\partial B_r/\partial x$); both were measured over the same site. The arrow on the head shows the approximate location and orientation of the equivalent dipole during N100m of the normal period. The insert on the right contains responses recorded with the 24-channel and 7-channel devices (24M and 7M, respectively); the 24M recording is the lower trace of pair 6. The main difference in N100m between the normal and hallucination periods is shaded.

## DISCUSSION

Patients who suffer from intense transitory hallucinations but are able to cooperate in research studies are hard to find. We had the opportunity to study two such patients, one with electric and the other with magnetic recordings. In both patients the auditory cortical responses were altered during the hallucination periods. Auditory evoked potential recordings from subject 1 revealed a delay of 20 msec in the peak latencies of N100 but no damping of the responses. In the magnetic recordings of subject 2, similar response delays were observed. The effects were small but replicable. During hallucinations, especially the early part of N100m was dampened, thereby causing the observed peak delay.

The magnetic N100m is evidently generated at the supratemporal auditory cortex (9). At the interstimulus intervals used in the present study, the amplitude and latency of N100m are very resistant to changes in the state of attention: the modification of the evoked responses due to attentional shifts starts only after N100m (10). Therefore, the observed latency differences of about 20 msec cannot be explained by changes in attention. Rather, the delay resembles the effects of speech and music maskers on responses to probe tones in healthy subjects (6). Auditory hallucinations may thus modify activity of the human auditory cortex in a way that is similar to how real (physical) masking sounds do so. Consequently, it seems possible that the auditory cortex is activated during hallucinations not by external input from the ear but by endogenous neural firing.

Retrieval of auditory memories is associated with interaction of the auditory cortex and the mesial temporal lobe, including the amygdala and hippocampus (11). Hallucinations might be caused by malfunctioning of these connections: morphological and imaging studies of schizophrenic patients (12–14) have revealed disturbed cytoarchitecture in parahippocampal areas and atrophy of anterior hippocampus and superior temporal gyrus. The hallucinations reported by schizophrenic patients are typically familiar sounds, such as words or music. Similar "acoustic memories" can follow electric stimulation of the auditory associative cortices, whereas stimulation of the primary auditory cortex elicits perception of elementary sounds, such as buzzing (15). Hallucinations in schizophrenic patients are therefore more likely associated with a distorted interplay between auditory associative areas and the limbic structures, rather than with a malfunction of the primary auditory cortex itself.

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# Book Forum

### Nancy C. Andreasen, M.D., Ph.D., Editor

## TEXTBOOKS

**Oxford Textbook of Psychiatry, 2nd ed.,** *by Michael Gelder, Dennis Gath, and Richard Mayou. New York, Oxford University Press, 1989, 1,028 pp., $95.00; $45.00 (paper).*

Often lost sight of in today's hectic academic life is the question of what we are trying to accomplish. Certainly, in the minds of most academicians, we are attempting to turn out true professionals whose careers are based on sound and broad knowledge and who have the highest ethical principles and great enthusiasm for their work. To do this, we must have a concept of the breadth, scope, and origins of our profession. In the United States we tend to be rather provincial and believe that we are the world's leader. In truth, we probably are at the forefront of many medical advances, but we have done this with the help of our forebears and our colleagues throughout the world.

Reading the second edition of the *Oxford Textbook of Psychiatry* would go a long way toward rectifying our provincialism. This book presents the scope of British and European psychiatry in a way that few of our trainees have experienced. The textbook has grown from its first edition in 1983 from 883 to 1,028 pages. It is an eminently readable book.

Diagnostically, the authors have chosen to use a draft of the new *ICD-10* nomenclature as well as *DSM-III-R,* which makes the text very useful for audiences in the United States. The overall organization of the book is by diagnostic categories and by specific topics. There are four excellent introductory chapters: "Signs and Symptoms of Mental Disorders," "Interviewing, Clinical Examination, and Record Keeping," "Classification in Psychiatry," and "Aetiology." Chapters on specific diagnoses follow: "Personality Disorder," "Neurosis I," "Neurosis II," "Affective Disorders," "Schizophrenia and Schizophrenia-Like Disorders," and "Paranoid Symptoms and Paranoid Syndromes." "Organic Psychiatry," a splendid chapter, is next, followed by chapters on such topics as psychiatry and medicine, suicide, substance abuse, sexuality, the elderly, mental retardation, forensics, and various treatments.

The book is extremely well written and generally exposes U.S. audiences to traditional concepts as well as concepts that, I fear, are rather "foreign" to us. A good example of the book's comprehensiveness and structure is the chapter on personality disorder. There is an excellent discussion on the assessment of personality and what "abnormal personality" means, a brief but comprehensive section on the history of the term "abnormal personality," and then various classifications and types of personality disorders. There is a brief paragraph on Sjobring's classification, which, I am sure, is unknown to most readers in the United States, followed by a very nice discussion of the general causes of personality disorder that covers such areas as genetics, body build, relation to mental illness, the various psychological theories related to personality disorder, and studies on personality development. With regard to the causes of personality disorder, there is an excellent section on antisocial personality that covers genetic causes, cerebral pathology, childhood behavior problems, and learning theory.

There is no question in my mind that every house officer in the United States would profit from spending several evenings with this textbook. Although it is short on cutting-edge topics such as neuropeptides, molecular biology, and imaging, it more than compensates with its breadth, scope, and clinical phenomenology. In this sense, this text augments our usual teaching and exposes us to the European literature that conveys the breadth and history of our field. It is this perspective that can separate the true professional from the pedestrian worker.

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**American Psychiatric Press Review of Psychiatry, vol. 8,** *edited by Allan Tasman, M.D., Robert E. Hales, M.D., and Allen J. Frances, M.D. Washington, D.C., American Psychiatric Press, 1989, 613 pp., $49.95.*

An excellent reference book for the practicing psychiatrist, this volume has been written for clinicians by recognized experts in the fields of adult psychiatry, child psychiatry, and alcohol abuse to provide in-depth reviews of selected current topics. The textbook is divided into five sections reflecting areas of clinical interest that have been chosen as the subject for intensive review in this edition: Borderline Personality Disorder, Child Psychiatry, Alcoholism, Psychiatry and the Law, and Difficult Situations in Clinical Practice. Each section features a foreword and afterword by the section editors, and each chapter ends with a fairly extensive bibliography.

John G. Gunderson, editor for the Borderline Personality Disorder section, has assembled a series of detailed and scholarly review articles on the epidemiology, pathogenesis, course, and treatment of this disorder. Cognitive-behavior therapy and pharmacotherapy of borderline personality disorder are two burgeoning areas of clinical interest addressed by the authors.

The Child Psychiatry section, edited by Jerry M. Weiner, provides a valuable overview of a number of commonly encountered psychiatric disorders of children and adolescents. The section's limitations appear to be principally a function of child psychiatry's lag in diagnostic refinement and the relative dearth of pediatric epidemiologic studies.

The genetics, epidemiology, neurobiology, and treatment of alcoholism are the subjects of the volume's third section, a collection of state-of-the-art reviews edited by Roger E. Meyer. The prominence of law and its relation to psychiatry provide the focus for the fourth section, edited by Paul S. Appelbaum. This section covers important territory related to issues of psychiatric malpractice, competency, informed consent, involuntary treatment, criminal responsibility, and child psychiatry and the law.

The volume's final section, Difficult Situations in Clinical Practice, edited by William H. Sledge, explores from a psychodynamic perspective some of the prominent sources of strain in psychiatric practice. It deals with issues of countertransference, psychiatric malpractice, the VIP patient, the violent patient, and psychiatrists' reactions to the death of a patient by suicide. The authors extend collegial advice and wisdom derived from clinical vignettes and scholarship as well as their own personal experiences in working with patients.

The volume is surprisingly short on contributions by women. Of the 54 editors and authors, nine of the authors and none of the editors are women. The obvious dominance of male contributors may affect decisions about what areas are reviewed as well as the way subjects are presented for discussion—particularly as they affect female patients and clinicians. Invitations to participate in volumes such as this annual review are important to women in academic psychiatry, whose career advancement may depend on developing name recognition and accruing publications.

Except for the potential for gender bias, this book has few serious faults in its writing and scholarship. The overriding concern of the volume's editors is to provide an outstanding reference text for the practicing clinician, a goal they patently achieve. I enthusiastically recommend this volume to residents, practicing psychiatrists, and other mental health professionals who would benefit from the in-depth reviews offered by these distinguished researchers and clinicians. Given its merits, the volume is well worth the price.

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**Handbook of Outpatient Treatment of Adults: Nonpsychotic Mental Disorders,** *edited by Michael E. Thase, M.D., Barry A. Edelstein, Ph.D., and Michel Hersen, Ph.D. New York, Plenum, 1990, 700 pp., $85.00.*

In their preface to this book the editors contend that a confluence of clinical, sociopolitical, and socioeconomic developments in mental health care have made outpatient services "the greatest area of growth" in the field of psychiatry. This *Handbook* was meant to be a "timely and useful" guide to outpatient diagnosis and treatment.

Distinguished contributors, diverse in disciplines and treatment approaches, have written 29 chapters covering the problems and disorders of patients as well as the techniques and concerns of clinicians involved in modern outpatient practice. The book is divided into four sections. In part one, five chapters review general issues of interviewing and diagnosis, differentiation of physical from psychiatric disorders, and drug, psychodynamic, and behavioral treatments in the outpatient setting. Part two contains 14 chapters describing specific disorders, usually concordant with *DSM-III-R* classes of disorders or specific diagnoses. Some departures in content are evident, however, in that chapters on chronic depressive disorders (rather than dysthymia), male sex offenders (instead of paraphilias), and problem drinking (not alcoholism) are included. Part three describes special clinical populations. There are chapters on marital dysfunction, adolescents and young adults, the elderly, Vietnam veterans, mentally retarded adults, and mentally ill substance abusers. The *Handbook* concludes with part four, which contains chapters on ethical and legal issues, the suicidal patient, office practice, and outpatient clinical research.

Although not totally standardized, the individual chapters are generally structured around themes of history, epidemiology or etiologic considerations, diagnosis and differential diagnosis, frequent clinical problems encountered, and specific treatment approaches. I found the chapters to be uniformly high in quality, rich in clinical detail, scientifically sound, and well referenced with extensive, up-to-date bibliographies. Most chapters include very specific suggestions for diagnostic workup and for treatment. For example, chapter 6, "Mood Disorders," includes a step-by-step guide to the outpatient management of treatment-resistant depression. Chapter 9, "Panic Disorder," has a decision tree for a treatment strategy for panic disorder. Chapter 11, "Sexual Dysfunction," gives flow charts for the evaluation of sexual desire problems and erectile dysfunction. Chapter 16, "Alzheimer Disease and Other Dementias," has a table of management techniques for common behavior problems among persons with dementia. Chapter 17, "Selected Organic Brain Syndromes," has tables for reported medical etiologies of delirium, organic delusional syndromes, organic affective syndromes, and organic anxiety syndromes. The chapters on special populations are noteworthy for their emphases on modification or adaptation of standard treatment approaches for patients with special needs.

The coverage of *Handbook of Outpatient Treatment of Adults* is clearly comprehensive. The only patient group arguably not covered are outpatients with chronic schizophrenia, many of whom undoubtedly are maintained and managed in clinics, mental health centers, and community outreach programs after deinstitutionalization. Some clinicians might also wish to have had a chapter on the treatment of personality disorders other than borderline and antisocial, which are discussed. The only other shortcoming of the book is its index, which does not include entries for monoamine oxidase inhibitors or lithium. It is a shame that the practical information filling the pages of this book is not made more easily accessible by a more useful index.

Overall, however, this is a valuable book. For reading and for reference, this *Handbook* deserves a convenient spot on the bookshelf of the clinician in office-based practice.

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## NEUROLOGY

**Synopsis of Neurology,** *by Richard Lechtenberg, M.D. Philadelphia, Lea & Febiger, 1991, 159 pp., $19.75 (paper).*

In *Synopsis of Neurology,* Richard Lechtenberg, author of *The Psychiatrist's Guide to Diseases of the Nervous System* (1), emphasizes that "the progression of deficits [with neurological problems] is as important as the character of the deficits." His outline of the neurological examination is succinct and generally adequate. We used to include the Chvostek sign, now obsolete because there is no rickets. In cases of syncope, we would gingerly stimulate the carotid sinus.

The elements of history and physical examination occupy 12 pages, and the next 15 pages recommend types of imaging and other laboratory procedures. Ultrasound is left out. Amytal interviews are recommended to establish the integrity of speech, but the scope of Amytal interviews is broader than that. Clinicians and patients deserve wider knowledge of this fairly safe technique.

A compendium is necessarily brief, but some facts in this book are dispersed or conflicting. For example, we are told that pathologies in various parts of the brain can cause anomial aphasia, but later the author says that severe anomias come from a lesion of the left anterior temporal lobe. In 1937 the latter fact was crucial in our diagnosis of George Gershwin's glioblastoma.

We are also told that hypomagnesemia can cause convulsions. In reference to eclampsia, however, the author calls the use of magnesium sulfate "inappropriate" for the "seizures." At Los Angeles General Hospital, where magnesium sulfate injections for eclampsia were initiated by Emil Bogen in 1924, this is still standard treatment, along with emptying the uterus. Dr. Lechtenberg tells us that carbamazepine is a relatively safe medication for the treatment of epilepsy in a pregnant woman.

He also asserts that neurological abnormalities due to thyroid deficiency are all remediable by thyroid substitution. We beg to differ. Pat Brownstein demonstrated years ago that cretinism can be corrected by thyroid if it is administered very early. If endocrine therapy is delayed to 3 months, however, the baby's chance of normal intellect is reduced, and it is further reduced the later the thyroid is started.

The author calls attention to intrauterine rubella infections as the cause of childhood defects, including what Leo Kanner called autism. Unfortunately, immunization against German measles is not universal, and the incidence of viral encephalitis has hardly decreased. We understand that the vulnerable period is the second trimester of pregnancy.

This book covers Alzheimer's disease adequately but fails to point out that memory or other deterioration typically begins before the age of senility. Dr. Lechtenberg properly warns that, "if the disease occurs before the age of 60, brain biopsy may be necessary to exclude treatable causes of dementia."

Parkinsonism is given almost current coverage. The International Parkinson Conference offers "hope . . . that fetal dopaminergic cells may represent a . . . source of [transplanted] tissue able to grow and compensate for the lost dopaminergic neurons in the Parkinsonian brain." Tissue transplantation for parkinsonism was also the subject of many papers scheduled for the 1991 meeting of the American Academy of Neurology. Although Dr. Lechtenberg displays a good knowledge of Wilson's disease, he omits the characteristic "rhisus sardonicus" and "wing flapping."

*Synopsis of Neurology* is a bit short on therapy. The new botulinum toxin treatment is of interest in the treatment of movement disorders. It is injected locally for dystonia, torticollis, writer's cramp, and blepharospasm. Presumably it acts solely at the neuromuscular junction.

In the excellent section on stages of sleep in the chapter "Sleep Disorders," credit is due to the discoverer of sleep stages, Nathaniel Kleitman. We wonder if sexual tension or stress is not a cause of "insomnia" and if sexual release is not a natural and effective treatment if there is no organic causal disturbance.

Dr. Lechtenberg devotes a paragraph to poliomyelitis, even though it has been practically eliminated in the United States through the use of two vaccines. Multiple sclerosis is well covered; the author published a fact book on the subject in 1988 (2). We used to suspect multiple sclerosis from a triad of scanning speech, bitemporal pallor, and intention tremor. Some still consider the CSF specific.

Dr. Lechtenberg's advice on subdural hematoma is astute. We too watched for late lapses into drowsiness or unconsciousness; inequality of the pupils was our signal "to go in."

We may have misunderstood the remark about the transiency of headache and hypertension from pheochromocytoma or the combination of monoamine oxidase inhibitors and tyramine-containing foods. These are dangerous situations, requiring instant antihypertensive medication and removal of causative agents.

A minor matter—those of us who know the imposing personality of Foster Kennedy do not put a hyphen between Foster and Kennedy. As for tinnitus, one is led to look for serious involvement of the eighth nerve, but many mild cases of tinnitus are best ignored. Strangely, in the chapter "Congenital Disorders," no specific reference is made to inborn errors of metabolism or amino acid deficiencies, such as phenylketonuria, although these are implied.

Happily, the author does address ataxia telangiectasia. Elena Boder has described these cases through many years. Their origin is now localized to chromosome 11.

There are many other fine chapters. *Synopsis of Neurology* is the distillate of an apparently wise clinician's expertise. Keep a copy of the paperback handy in your briefcase or examination kit. We will do likewise, and we look forward to meeting Dr. Lechtenberg somewhere sometime.

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**Merritt's Textbook of Neurology, 8th ed.,** *edited by Lewis P. Rowland, M.D. Philadelphia, Lea & Febiger, 1989, 928 pp., $67.50.*

A book that appears in its eighth edition must have a great deal to recommend it. The first edition of this book (1955) and the next five editions were prepared entirely by Professor Merritt himself. He died in 1979, and the present book is a fitting memorial to him. The tremendous influence of Dr. Merritt on neurology in the United States is demonstrated by the 70 contributors who were his students, 30 of whom have become heads of departments or professors throughout the country. The march of progress threatens to make obsolete this textbook, like all books, requiring more frequent revisions, but since the introduction of magnetic resonance imaging (MRI), the AIDS epidemic, and Lyme disease, little has occurred that would render useless a text that is only several years behind the times. For example, the explosion of molecular genetics occurs at too great a rate for even monthly journals to keep pace, but *Merritt's Textbook of Neurology* provides a solid background against which the new discoveries may be organized.

This volume starts with a section entitled Signs and Symptoms of Neurologic Disease that includes delirium and dementia; aphasia, apraxia, and agnosia; syncope and seizure; coma; pain and paresthesias; dizziness and hearing loss; impaired vision; headache; involuntary movements; syndromes caused by weak muscles; gait disorders; and "signs and symptoms in neurologic diagnosis." Following this section, the book is organized around disorders rather than anatomy. First the conditions of known etiology are presented, including infections, vascular diseases, tumors, trauma, birth injuries, and genetic diseases. Then the neurological disorders of uncertain etiology are discussed, including particularly good sections on cerebral degenerations of childhood by Isabelle Rapin and on movement disorders and spinal cord disorders by authorities of the stature of Stanley Fahn and Rowland himself.

The discussions of head injury, cerebral palsy and mental retardation, autism, and pain syndromes are particularly lucid and useful for psychiatrists.

This is not a "how-to-do-it" book but assumes knowledge of the neurological examination, neuroanatomy, and various laboratory procedures of neurology. There are excellent illustrations of CT scans and MRI scans that have been updated by the Radiology Division of the Neurological Institute of New York.

Inevitably, a text must be compared with other texts, and the necessary deficiencies of an edited book with many authors must be weighed against the advantages of having 70 experts produce essays in their areas of expertise rather than having one person try to cover a field as vast as the human nervous system. *Neurology* by Mark Mumenthaler (1) is also organized around diseases and has been a standard text in Europe since the first German edition in 1967. *Merritt's Textbook,* on the other hand, is a distinctly American book. Mumenthaler's *Neurology* is written by a Swiss professor and has been published in 10 languages to date. *Merritt's Textbook* lacks the beautifully diagrammatic neuroanatomical illustrations and the emphasis on practical physical diagnosis of Mumenthaler's *Neurology.* One might have the best of both worlds by getting *Merritt's Textbook* for its state-of-the-art discussions of pathology and biochemistry and supplementing it with *Neurologic Differential Diagnosis* by Mumenthaler (2), which is a short (156 pages with index) volume of syndromes and symptoms diagramed in functional neuroanatomical detail with tables and charts that would allow a reader with even rudimentary knowledge of the physical examination to become expert in neurological diagnosis. *Merritt's Textbook* would be most useful to psychiatrists who wish to be informed about diseases of the nervous system, but it would not provide enough information to the novice to allow hands-on diagnosis or treatment of patients with neurological problems. That is not necessarily a flaw because the text is a reference rather than a tutor. *Merritt's Textbook* makes excellent reading, and it is remarkably inclusive for a standard-size book.

Although neurology is thought of as "hard" science, it soon becomes clear that this specialty lacks a diagnostic and statistical manual. It also lacks the controversies that go along with attempting to find such a consensus. *Merritt's Textbook* does not touch the active debate going on regarding the international classification of headaches. It also essentially steers clear of the most important functions of the brain—thought, emotion, and human consciousness—except in the introductory chapters, where the treatment of "behavioral neurology" is quite inadequate for the practicing psychiatrist who wishes to understand the complicated relationships of brain and behavior that are perturbed by human disease. Lishman's *Organic Psychiatry* (3) is a necessary companion to either *Merritt's Textbook* or Mumenthaler's *Neurology.* There is as yet no textbook that discusses the higher cognitive and emotional effects of the hundreds of known neurological syndromes. Those wishing to perform their own synthesis of brain and mind would be well-advised to use *Merritt's Textbook of Neurology* as an authoritative background reference.

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## CHILD PSYCHIATRY

**Concise Guide to Child and Adolescent Psychiatry,** *by Mina K. Dulcan, M.D., and Charles W. Popper, M.D. Washington, D.C., American Psychiatric Press, 1991, 241 pp., $21.00.*

I was skeptical about the idea that a pocket-sized text could offer a clinically useful and comprehensive overview of the most salient aspects of child and adolescent psychiatry. Concise guides more often seem suited to books on travel and home repair. However, the authors have produced an excellent resource for beginning clinicians as well as for those with more experience who only occasionally see children with psychiatric problems.

The authors begin by reviewing general issues in the evaluation and treatment of children and adolescents with psychiatric disorders. This section offers a brief orientation to the unique aspects of child psychiatry and is loaded with useful clinical information—from play materials that may facilitate a more comfortable interview (e.g., washable markers) to tables summarizing the instruments available for intelligence and academic testing. The next several chapters review the clinical features, epidemiology, etiology, course, prognosis, evaluation, differential diagnosis, and treatment modalities for axis I disorders. The sections on clinical features are informative and clear, but the sections on etiology may suffer from the concise guide format. The chapter reviewing schizophrenia and disorders of substance use, mood, anxiety, sleep, and adjustment is brief and probably does not reflect the relative importance of these disorders in the practice of child psychiatry. The last three chapters cover special clinical circumstances (e.g., emergencies, divorce, and chronic medical illness in children), psychopharmacology, and psychosocial treatments. The chapter on psychopharmacology is perhaps the best suited to the concise guide approach and will be particularly helpful to general psychiatry residents wrestling with medication doses for children. Together, these three chapters present a wide range of relevant information on assessment and treatment in a clear and easily accessible format. Finally, the authors include an appendix for parents, referencing books on problems that range in severity from sibling rivalry to schizophrenia. This is a book to be used, not one to be relegated to a space on the shelf.

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**Recognizing Child Abuse: A Guide for the Concerned,** *by Douglas J. Besharov. New York, Free Press, 1990, 270 pp., $24.95.*

Reviewing books is a snap. All you need is catholic reading tastes, good typing skills, and a titanium-lined digestive system. Strong stomach? In this case, yes. *Recognizing Child Abuse* is an unusual work that uses gut-wrenching text and pictures to present nearly everything needed to deal with children who have been neglected, physically abused, or sexually assaulted.

After an introductory overview (more than 2 million reports of child abuse were made in 1987) we learn the legal pitfalls of whom, what, and when to report; the rights and responsibilities of the reporter; and the likely consequences should the duty to report be neglected.

Much of the information is bundled into charts (48 of them), handy for a quick review. Chart 3-2 spells out what must be reported—a dozen types of abusive behavior, including neglect to respond to a child's emotional and educational needs. Although under 10% of reports are knowingly false, hot lines are often clogged with instances of delinquency, truancy, and other behaviors outside the intended scope of the statutes. Another chart lists conditions of poor environmental conditions that are often overreported as neglect.

A major problem for professionals and lay persons alike is discriminating abuse from reasonable punishment. Chart 7-1 helps with this problem. The author also discusses frequently observed "suspicious" injuries, categorized by age of child, and provides illustrations courtesy of John Craig and CIBA. This section is not for the faint of heart.

Sexual abuse is examined from the twin perspectives of the physical evidence and the victim's behavior. The author cautions us not to use the latter alone as the basis for making a report—children can be excessively shy or overly friendly for reasons other than abuse.

Besharov is a consummate advocate for children. He would take preventive action when a parent appears incapacitated by schizophrenia or severe depression. This approach may make some patient's rights advocates squirm. Not surprisingly, he backs up his arguments with several charts, including a listing of suspicious behaviors that might be observed on a maternity ward.

Later chapters explain how to make a report (what to include or leave out) and how to preserve evidence. The author advises parents on how to seek help if they suspect a child is being abused or if they themselves are reported for abuse.

If this book has a flaw, it is that it is sometimes encyclopedic without being specific. For example, it states that laws in half the states allow medical professionals to hold endangered children but does not say which half. I wanted a table (surely, the author must have had one more chart in him) comparing the requirements of different jurisdictions. There is an appendix listing child protective agencies in 54 states and territories.

*Recognizing Child Abuse* is a thorough, compelling, and readable work that I strongly recommend for any professional who treats children or their parents. But keep the antacids handy.

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**Clinical Aspects of Child and Adolescent Development: An Introductory Synthesis of Developmental Concepts and Clinical Experience, 3rd ed.,** *by Melvin Lewis, M.B., B.S., F.R.C.Psych., D.C.H., and Fred R. Volkmar, M.D. Philadelphia, Lea & Febiger, 1990, 445 pp., $42.40.*

Books become classics when they provide essential information, maintain timeliness, are well received by an audience, and offer insights not obtainable from other sources. *Clinical Aspects of Child and Adolescent Development* can be considered among the classic textbooks in child and adolescent psychiatry. This is the third edition of the text, which was originally published in 1971 with the goal of providing the medical student with "an introductory synthesis of certain basic psychological concepts and their use in understanding the wide range of behaviors seen during the stage of human development we call childhood" (p. vii). The third edition has been updated and extensively revised. The text follows a pedagogical concept that "views medical education as a kind of spiral process, in which the student first goes once over lightly, and relatively briefly, the broad sweep of the curriculum. At subsequent periods he can then go over similar ground, this time with more familiarity and greater depth" (pp. vii–viii). The preface to the third edition notes that the theoretical framework for this book is based on the "struggle with the multiple theories we now have to account for human behavior. Explorations of the biology of the cell and the psychology of the unconscious continue to account for bits of human behavior, in some cases better than in others" (p. ix).

The book describes longitudinal, cross-sectional, and developmental perspectives of normal and pathological development and focuses on pediatric and psychiatric disorders and treatment. This third edition enlarges the scope of developmental processes to integrate descriptions of childhood and adolescence. The book is very comprehensive and remarkably easy to read. The text is specific and brief and clearly explains concepts in an objective way. A unique feature is that at the end of most chapters, brief annotated notes are included to illustrate statements from primary source books or papers. The authors' purpose was to expose students to concepts presented by theoreticians, researchers, and clinicians who have made major contributions to the field of child development and psychiatry. There are ample figures, tables, and illustrations that emphasize concepts and make it possible for a student to more easily synthesize the material and gain a greater depth of understanding.

A number of other features of the text are noteworthy. Chapter 23, "The Psychiatric Evaluation of the Infant, Child, and Adolescent," is a comprehensive review of factors to be assessed during a mental status examination of children or adolescents. This chapter can be useful as a guide for both inexperienced and experienced clinicians to organize a complete mental status examination. The chapter on differential diagnosis presents the rationale of why formulating a differential diagnostic assessment in children is so difficult, especially since diagnostic classification has not been sufficient to capture precisely the entire spectrum of child psychopathological presentations. Other problems in diagnosis include reliability of informants and lack of reliable measures of childhood symptoms. The chapter attempts to discuss a number of diagnostic issues such as attention deficit disorder, bed wetting, hallucinations, language and speech dysfunction, reading difficulty, seizure behavior, sleep disturbances, spelling difficulties, stealing, temper tantrums, social isolation, thought disorder, and violent behavior. However, it omits such important problems as depression, anxiety, and eating problems.

The chapters on childhood and adolescent psychopathology clearly present highlights of specific syndromes that nicely complement previous chapters on assessment and differential diagnosis. The two chapters on treatment outline features of psychodynamic psychotherapy and psychopharmacology. Concepts of interpretation during psychotherapy and psychotropic-prescribing guides are presented informatively, clearly, and concisely. A shortcoming evident throughout the text, however, is that a greater number of more recent references could have been provided. Nevertheless, the scope of material covered is pertinent and up-to-date.

In summary, this text should continue to be considered a classic. There are few textbooks that address the needs of students with beginners' backgrounds in child and adolescent development and psychopathology. This book strongly meets the need for education, review, and synthesis. Dr. Lewis is a skilled and outstanding teacher and clinician, and Dr. Volkmar, who joined Dr. Lewis in writing this third edition, has helped to widen the scope of the material. I highly recommend this book, which should be especially available in medical school libraries.

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**Giant Steps: Therapeutic Innovations in Child Mental Health,** *by Lee Combrinck-Graham. New York, Basic Books, 1990, 291 pp., $27.95.*

The central thesis of this book is that there currently exists a crisis in the delivery of mental health services to children. According to the author, the reason for this state of affairs is that there are more children in need of treatment than there are available qualified service providers. To surmount this problem, she advocates a reconceptualization of mental health within a systems theory perspective. At the practical level, major innovations in treatment are required; these innovations are referred to as giant steps.

The book consists of three main sections. Part one focuses on childhood development with respect to proximal and distal social systems surrounding the child. The first giant step, according to the author, requires recognizing that there are multiple realities encompassing different aspects of the person's experience. Thus, to effectively address mental health problems, differing perspectives obtained from various vantage points need to be integrated into interrelated and meaningful systems. This section of the book advocates that application of the systems theory framework to diagnosis and treatment be the first step in resolving the mental health service delivery crisis.

Part two elaborates on the contextual basis of psychopathology as well as its diagnosis and treatment as discussed from the systems theory perspective. Particular emphasis is placed on the family system. The giant steps here pertain to evaluating and recasting the components of the system promoting psychopathology or behavior disorder.

Part three examines key macrosystems—the health, legal, social, and educational environments in which mental health disturbances need to be identified and treated. Numerous case anecdotes, buttressed by the author's personal opinion, are interspersed in the discussion. This aspect of the discussion frequently has a polemic quality. Although the author is to be commended for emphasizing the contextual basis of mental health problems in children and applauded for suggesting the need for giant steps, she unfortunately offers no plan for implementing changes. She offers only the pessimistic conclusion that the needed changes are not likely to happen in the foreseeable future. The fact of the matter is that major initiations currently underway are devoted to developing an integrated systems approach to mental health problems.

The main contribution of this book is its emphasis on person-environment interaction. This may appear mundane; however, the reader is reminded that psychiatry today emphasizes the biological mechanisms underlying psychopathology without a complementing emphasis on the psychosocial environment. The poor quality of fit between the person and the environment as the primary basis of maladjustment is not well integrated in current diagnostic and treatment practices. By advocating for the systems theory perspective and, accordingly, for a paradigm shift in diagnosis and treatment, this book makes a useful contribution.

Certain shortcomings of this book are notable, however. The author does not address issues and problems regarding the health policy environment and training needs of professionals. She gives virtually no attention to the research literature of the past two decades. Consequently, for the informed reader, the material presented in this book is superficial and lacking in critical analysis. It is sometimes difficult to decipher what the author means exactly. For example, in one paragraph under the heading "Acting Like a Mental Health Professional," she states, "Mental health is not a place and it is not a service." Two sentences later she exhorts professionals to "offer mental health services." The lack of precise communication weakens the book.

In sum, this book is a heralding call for a systems change rather than an empirical analysis of the problems associated with the diagnosis and treatment of psychopathology.

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## PSYCHOANALYSIS

**Psychoanalysis: Toward the Second Century,** *edited by Arnold M. Cooper, Otto F. Kernberg, and Ethel Spector Person. New Haven, Conn., Yale University Press, 1990, 220 pp., $27.50.*

This book celebrates the 40th anniversary of the Columbia University Psychoanalytic Center. This psychoanalytic institute, one of few within a university, has represented a liberal pole in the debate between right- and left-wing theorists in the issue of whether to replace Freud's early libido theories. This debate leads to four domains for new theories, each a section in this book: Culture, Drives, Self, and The Interface of Mind/Brain Levels of Explanation.

Libido theory started with an evolutionary slant on sexual drives. Later, the person was seen as enmeshed in a social field that imposed psychological sexuality on the biological core of instinct. Culture had to be considered. By a courageous refusal to accept dogma, Rado, Kardiner, Levy, and Daniels—founders of the Columbia Institute—established a path of integration among individual psychology, psychoanalysis, and social disciplines such as anthropology.

Psychoanalysis brings its own observations to this intertheoretical effort. Transference phenomena are an example. In the section on culture, Person beautifully details how clinical supervision and transference patterns replicate across social frames of treatments and training. Also in this section, Kernberg describes how social processes such as repetition of political frustrations in the mass media can affect the individual in terms of progression and regression in views of self and others. One result may be evocation of a regressive yearning for an idealized leader. That can lead to endorsement of leaders whose paranoia and narcissism then assume malignant proportions through ascension to unchecked political power.

In the second section, Drives, Cooper rejects the early psychoanalytic explanation of emotions as derivatives of instinctual drive energies as too limiting for modern and future theories. Karush describes three new hypotheses within current psychoanalytic theory: emotion as part of all ideas and personal schemata, complex affects as signals and symbols, and the power of figures of speech to redirect the expressions and representations of emotionality. Sandler summarizes complex motivation theory as including goals of safety and control over states of mind. Viederman points to the role of ideals, self-schematization, and desires to change as effectors of mental activities and life-planning choices. The section on drives ends by setting the stage for chapters in the next section.

In the third section, Self, Meyers shows how Freud's language contains many modern concepts of self. Michels, Schafer, and Stern each presents a separate point of view. All point to future theoretical developments that can handle issues of multiple self-schematization in a single individual and the development of supraordinate meaning structures.

The final section deals with the mind/brain. Person reviews the mind/body dilemma of philosophy, setting the stage for Cooper's final chapter, a fine refutation of neurocomputational reductionism.

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**Psychoanalytic Knowledge,** *by Eugene B. Brody. Madison, Conn., International Universities Press, 1990, 246 pp., $30.00.*

This is a puzzling book that analyzes psychoanalysis from outside and inside at the same time. Many defects of the psychoanalytic system are delineated with clarity: its dependence on an archaic psychobiology, the resemblance of psychoanalytic organizational structure to that of an organized religion, the importance of hierarchical structure as an impediment to sober challenge, the economic forces that reward individual psychoanalysts for creating new co-religionists who themselves must find new acolytes in order to recover the cost of their education, and the tendency of a protracted and closely monitored training program to reward conformity rather than creativity, which is viewed as dissent or failure to comprehend.

Brody answers each criticism lovingly—all are valid, and each has meaning that must be understood within the system of psychoanalysis itself. All of these flaws, these contradictions between a professed openness to investigation and the rigid framework within which it may be expressed, are evaluated in terms of the profound benefit to be achieved by immersion within the system. We learn here that a rigid orthodoxy may protect a fluid discipline, that each worker deserves reasonable pay, and that newer science allows us to replace archaic theory with modern reason while still retaining the beauty of the original construction. This is a lover's book, full of the joy to be experienced when one gives up resistance and dives into the unknown accompanied by a psychoanalytic guide.

One cannot ask for a more articulate introduction to the dilemma in which modern psychoanalysis is caught up. The observer who remains outside the fold must see psychoanalysis as a template, a structured mode of inquiry that offers powerful understanding even as it distorts the field it views. Not to know its special contribution is to remain naive, ignorant of the inner world that governs so much of our experience. Such understanding may not be possible without the willingness to accept theories and rationales that are clearly flawed, but those who do accept, join, immerse themselves, and eventually belong seem inevitably to lose their ability to step outside the system and see explanations, treatments, and, indeed, world views impossible from within.

Like most articulate and intelligent members of the psychoanalytic community, Brody has his own system of patches to place on this leaky vessel. Suggested is an information processing model for the unconscious and an anthropological outlook that takes this adjustment of theory into the larger community. Everywhere Brody is interesting and informative, scholarly and entertaining. Yet the entirety of this slim volume serves to justify the author's assertion that *Psychoanalytic Knowledge* is available only from within the fold of psychoanalysis.

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**The Human Core: The Intrapsychic Base of Behavior, vol. 1,** *by Leo Rangell. Madison, Conn., International Universities Press, 1990, 478 pp., $60.00.*

**The Human Core: The Intrapsychic Base of Behavior, vol. 2,** *by Leo Rangell. Madison, Conn., International Universities Press, 1990, 500 pp., $60.00.*

A generation of psychoanalysts and psychoanalytically oriented clinicians in the United States looked to the ego psychology "school" of Anna Freud and the triumvirate of Hartmann, Kris, and Loewenstein and their disciples as the leading edge of the true Freudian doctrine. It is to this generation that Leo Rangell belongs and it is in this doctrine that his "core" is centered. *The Human Core* comprises selected papers by Rangell that he believes reveal a connected theme, namely, the ongoing unconscious intrapsychic process. He has a particular interest in what he describes as the unconscious decision-making function of the ego. His contribution is to elaborate the clinical and theoretical aspects of this "ego function." He also presents the related theme of structural levels of anxiety. At the first level is anxiety signaling an unacceptable impulse. This leads to some defense (e.g., repression), creating an oppositional conflict between ego and id. A second level of anxiety will arise if repression cannot deal with the state of increasing psychic tension. This second-level signal anxiety can in turn produce inhibitions, symptoms, and greater anxiety. Rangell believes that his structural theories (which I have by necessity grossly oversimplified) are a working out of the ideas of the later Freud, Hartmann, and David Rapaport. Rangell's goal is to use this structural approach to produce a psychoanalytic theory of action and to resurrect some psychoanalytic notion of will and of moral responsibility.

Certainly Rangell has chosen important theoretical objectives, but, unfortunately, I do not think he achieves them. For example, commenting on the legal issue of criminal responsibility, he suggests that his ego psychology would propose a spectrum of responsibility instead of the duality of responsible versus irresponsible. This idea is neither useful nor original, but Rangell seems to know that most of his potential audience has headed for the exits. By the time one gets to the end of these two volumes it is clear that Rangell is not happy about the state of things. Freud used to be in; now he is out. In "politically correct" circles, Freud is considered patriarchal, authoritarian, unfeeling, and doctrinaire, and so are Rangell's true Freudians. It is not just that potential patients are wary and that Freud is in bad odor, Rangell believes that ego psychology, a valuable scientific paradigm, is being destroyed from within by the negative paradigms of other psychoanalytic perspectives.

What Rangell seems unwilling to consider is the possibility that the many critics and defectors are correct in realizing that ego psychology is in fact a blind alley. The structural approach in its reification of human subjectivity understood everything and therefore understood nothing. Reified theory soon loses its explanatory power, and the "human core" thus understood has lost its defining capacity of surprise.

Freud's genius had an oppositional streak. He loved to stand things on their head and confound his readers' expectations. Indeed, as long as Freud lived he felt free to see afresh. One can quote Freud against Freud on many crucial issues. There is, therefore, no true Freudian doctrine; there is only the possibility of an encounter with Freud's genius. Those who dismiss Freud without reading him because he is no longer politically correct are Philistines. However, those who claim to quote the true Freud and preside over his temple are the pharisees.

Rangell has a human spirit too generous and searching to be cabined by the pharisee label. His own psychological and intuitive gifts as a psychoanalyst rescue him from the level emptiness of the ego psychology theory to which he has given his allegiance. One sees his gifts most clearly when he either shares his nuanced reading of Freud or reports his own clinical insights into his patients. Unfortunately, much of what he writes deserves to be ruthlessly edited, but the reader who perseveres will emerge from the thickets every few pages and catch a glimpse of something worth the effort. *The Human Core* is a defense of the true faith; it is unlikely to attract converts.

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**Drive, Ego, Object, and Self: A Synthesis for Clinical Work,** *by Fred Pine. New York, Basic Books, 1990, 269 pp., $25.95.*

Despite its many critics, internal controversies, and historical vicissitudes, psychoanalysis remains the mother of all personality and clinical theory. The longevity of psychoanalysis has guaranteed evolution in theorizing and the development of competing models for understanding what psychoanalysis is, the nature of its subject matter, and how it works. Competing understandings of what psychoanalysis is and the nature of its subject matter have been the sources of intense squabbles among psychoanalysts. The history of the psychoanalytic movement, not unlike religious movements, has had its shibboleths of orthodoxy and faithfulness to the vision of its founder and, in cases of divergence, accusations of heterodoxy, excommunications, and schisms. Freud's work itself contains many contradictions and revisions across his lengthy career, and, when examined closely, Freud's work lacks the internal coherence that one might rightly expect in a unified theory. Freud's models of the mind—the reflex arc, structural and topographical theories—are but one example. Many critics and psychoanalytic theorists have deplored the multiplicity, pluralism, and lack of theoretical unity in the discipline.

Rather than deploring psychoanalytic pluralism, Fred Pine sees the "four psychologies of psychoanalysis" as powerful tools at the service of the clinician. Pine takes the well-known history of clinical psychoanalysis—from classical drive theory and Freud's nascent ego psychology through ego psychology proper to the emergence of object relations theory and, finally, self psychology—and views these as alternating and interrelated perspectives for viewing and doing psychoanalysis and psychoanalytic psychotherapy. Pine stresses that any psychological event may be described from four functional points of view—in relation to drive gratification, ego functions, object relations, and self experience. Pine's thesis is that this multiplicity is a source of strength, and he sets out to demonstrate the usefulness of alternating frameworks for understanding human development, clinical concepts (for example, the concepts of motivation, ego defect, and preoedipal pathology), and work with individual patients. Rather than decrying their competing claims and perspectives, Pine sees them as tools at the disposal of the practitioner.

Pine's presentation of his argument is couched in a scholarly but jargon-free "experience-near" conceptualization, without contesting (or even addressing for that matter) the underlying assumptions and claims of each approach. The chapters on symbiosis and preoedipal pathology are especially rich. His approach, consistent with most modern psychoanalytic theory in the United States, is a sort of psychoanalytic psychology without metapsychology. The pragmatism and utilitarianism advocated here could, perhaps, have been written only by an American psychoanalyst.

Pine looks at personality development in terms of the four psychologies and through detailed vignettes of clinical cases, illustrates how "moments" in treatment (in the context of evenly suspended attention) can be alternatively conceptualized and serve as the basis for intervention. Indeed, Pine would have us believe that a complete analysis or psychotherapy may necessarily bring all of the perspectives to bear in work with the individual patient at one time or another.

Many, especially those deeply wedded to the assumptions and claims of one or another of the four psychologies, will find Pine's syncretism and leveling of these approaches objectionable and controversial. Others, especially trainees, who are not burdened by the baggage of loyalty conflicts and previous commitments, may find Pine's ideas quite compatible and not particularly revolutionary. One must admit, however, that each of the four psychologies does indeed have its own milieu, language, and technical variations. Again, not unlike religion, the true colors, feel, and nuances of a perspective or world view do not emerge unless viewed from a committed outlook.

I do not think that Pine's eclecticism is a substitute for immersion in the viewpoints espoused by the adherents of the four psychologies of psychoanalysis. Nevertheless, Pine's work is well written, clinically insightful, and very modern and provides the practitioner with the tools to broaden and deepen listening, understanding, and intervening.

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**The Annual of Psychoanalysis, vol. XVIII, 1990,** *edited by the Chicago Institute for Psychoanalysis. Hillsdale, N.J., Analytic Press, 1990, 231 pp., $29.95.*

This annual was a pleasure to review. It contains four sections that give a broad range of current ideas, predominantly focusing on a self psychology perspective. Although other theoretical perspectives are not included, I found the book very stimulating and would encourage psychiatrists to look at this annual and select articles of interest. All have substantial clinical relevance.

The first section, Developmental Studies, includes two papers. The first is on the developmental psychology of the self and the changing world view of psychoanalysis. The authors of this chapter review the evolution of classical psychoanalysis and Freud's assumptions, which were based on the scientific world view of his time. This evolution progressed to a "postmodern" view of science, which embodies a world view based on the study of individuals over time from the point of view of their own experiences rather than in terms of functions and mechanisms. The authors attempt to show how people maintain a sense of integrity by attending to an understanding of the subjectivity of the individual. They recommend making an empathic comprehension of meaning and motives the goal of psychoanalytic investigation. This is a very scholarly paper that brings the reader up to modern-day self psychology perspectives and to psychoanalysis in the 1990s. The other chapter in the first section is a very creative treatment of the interface of developmental psychoanalytic psychology and the changing understanding of the organization of the brain.

The next section includes four papers on clinical studies, including such areas of interest as what happens in therapeutic stalemates and what is the nature of the therapeutic interaction. A paper that should be of interest to many is one on varieties of therapeutic alliance by Brandchaft and Stolorow, who examine the bond between the analyst and patient, recognizing that the establishment of this bond is of primary importance in the conduct of good psychoanalytic work. In the ego psychology view, the understanding of resistance comes from conflict solely within the patient. The authors aptly state that ego psychology analysts require the patient to identify with the analyst's view of himself or herself as essentially neutral in relation to the patient's conflicts. The authors focus their arguments on the largely unchallenged assumption in ego psychology and object relations psychoanalysis that there is an objective reality known to the analyst. The authors acknowledge and elaborate on the work of Evelyn Schwaber in her focus on the importance of attending to the patient's subjective reality and the goal of the analyst's stance, which is to understand the experience of the analytic process from the patient's perspective.

The third section includes two papers. "Object Versus Self-Object Studies" by Estelle and Morton Shane addresses the process of mourning and contrasts object loss with self-object loss in both adults and children. The authors attempt to enrich our understanding of the importance of self-objects in mourning the loss of a significant other for adults as well as for children. The second paper contrasts the transitional object with the self-object concept in relation to the treatment of patients with borderline personality disorder.

The final section of this annual contains theoretical and historical contributions. There is a wonderful article on postanalytic amnesia, clarifying the normality of remembering very little of the therapeutic process. There are also two excellent papers on hypnosis and its relationship to psychoanalysis and on Freud's views as they evolved through his life as well as the concepts developed since Freud's time that reflect the changes in psychoanalytic theory. The final paper is an illustrative mathematical model of affects.

Overall, I found this book to be another major contribution to psychoanalysis. One who reads this annual will feel much more abreast of current psychoanalysis.

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## SEXUALITY

**Incest-Related Syndromes of Adult Psychopathology,** *edited by Richard P. Kluft, M.D. Washington, D.C., American Psychiatric Press, 1990, 293 pp., $32.00.*

We are most comfortable with patients who are most like us, treating them with empathic sensitivity and the profound respect we wish for ourselves. To those whose illnesses make them so unlike us that they may be regarded as barely human, we offer the surcease of purely somatic therapies, protective incarceration, and massive disavowal of their inner lives.

*Incest-Related Syndromes of Adult Psychopathology* is a passionate and disciplined book about a grubby little subject that nobody likes. Maybe it was acceptable to nod tolerantly and dismiss incest when we were taught that it "happened" in fewer than one in a million families. But there is no taboo against incest—there is only a taboo against talking about it. The real frequency? Perhaps nearly all of those with multiple personality disorder, many or most of our immense and growing population of male and female prostitutes, and a surprisingly high percentage of those with "borderline" personality disorder.

The editor of this book, Richard P. Kluft, has devoted his career to the study and treatment of those among us who have been the most damaged by actual psychic trauma. He has assembled a group of talented and dedicated clinician/scientists whose work now requires us to look for evidence of incest with an urgency directly in proportion to the amount of chaos seen in our cases. Kluft's opening chapter, itself of a literary quality rarely found in clinical texts, models the sort of self-examination necessary to the lysis of disavowal. It is not that we have never come across cases of incest, he says—they were the promiscuous sisters of our high school buddies, the "easy lays" of our own years of sexual yearning. In his closing chapter, Kluft drives home a message even more difficult to face—the experience of incest makes the victim a "sitting duck" for sexual interaction with teachers, therapists, and religious authorities. Whoever has been used sexually by his or her caregivers remains compelled to repeat such scenes of abuse until some careful clinician recognizes this form of seductiveness as a specific message within the transference.

Many of the other authors echo the editor's concern. Diane H. Schetky reviews the literature on long-term and late-appearing sequelae of childhood trauma. Bennett G. Braun demonstrates the relation between severe child abuse and dissociative disorders like multiple personality disorder; the average professional reader is likely to experience some dissociative symptoms on reading his chapter. Philip M. Coons et al. remind us of the many studies suggesting that nearly one woman in five has been coerced into sexual experience before age 13 and demonstrate the effect of such a history on later emotional function. Michael H. Stone, who has published so many careful studies of "borderline" personality disorder, reviews his data in terms of incest. Richard J. Loewenstein suggests that those who cannot talk about what has happened to them may express their pain as somatoform illness. Incest has been the secret trauma lurking behind an enormous fraction of our "untreatable" cases.

Where there is so much secrecy and so many dreadful, life-threatening defenses against a victim's knowledge of his or her personal experience of incest, the reader would expect much discussion of shame. Not so. Only one author (Rosalyn Schultz) mentions shame and in passing, at that. The immense and growing literature on shame (replete as it is with discussions of incest and other forms of sexual abuse) occupies a world far removed from these otherwise excellent authors. Throughout the book one is aware of a bias toward neocortical cognition, toward the alterations in thought patterns found in those who have been abused severely and terrorized by those who hold authority over them. Affect is discussed only in terms of its effect on cognitive function. Yet all of the syndromes discussed here are, at core, responses to overwhelming affective experience.

*Incest-Related Syndromes of Adult Psychopathology* is a breakthrough book that makes it impossible for any reader to ignore the ubiquity of sexual abuse. Brought into accord with the modern study of affect, it offers a new look at the ignored and powerful effects of misguided passion, of sexuality as power over a helpless other.

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**Adolescence and Puberty,** *edited by John Bancroft and June Machover Reinisch. New York, Oxford University Press, 1990, 279 pp., $39.95.*

This book is one in a series examining issues relating to sex, gender, and reproduction under the editorship of Dr. Reinisch, Director of the Kinsey Institute in Bloomington, Ind. This particular volume is an outgrowth of a symposium on adolescent sexuality and behavior held at the Institute in 1986. A variety of topics were covered: factors influencing the onset of puberty, the emergence of sexuality, the emotional changes associated with adolescence, patterns of sexual behavior, and certain legal aspects of the adolescent role. These are included in the book with a few more current references.

Many of the 26 contributors (mostly M.D.s and Ph.D.s) are careful to distinguish between adolescence and puberty: adolescence is a psychosocial stage of development, whereas puberty is a physical process characterized by hormonal changes and the emergence of secondary sex characteristics. Michael Rutter, Professor of Child Psychiatry at The Institute of Psychiatry in London, one of the book's most outstanding contributors, states that the stereotypical view that adolescence is a time of storm and stress characterized by emotional turmoil and psychic disturbance is incorrect. Most young people pass through adolescence without developing any form of substantial mental disturbance. This view was also held by Erik Erikson, who never intended the term "identity crisis" (also called "adolescent turmoil" by some workers) to be mistaken for mental disorder. It is a normative developmental stage that all adolescents must successfully negotiate before entering adulthood.

Following is a small sampling of some of the many findings about adolescence and puberty reported in the book: 1) Puberty is considered to be early if the first physical signs occur before age 8 years for girls and age 9 for boys and delayed if no physical signs appear before age 13 in girls and age 14 in boys. 2) Adolescent girls who live together develop synchronous menstrual cycles, usually within 3 to 4 months, possibly as a result of pheromonal stimulation. 3) Coital behavior of males is highly hormone dependent, whereas that of females is mainly related to social effects and learning. 4) Almost 20% of teenage girls in the United States have an abortion before reaching 20 years of age. 5) The teenage birthrate is much lower in those parts of the world (e.g., the Flemish-speaking part of Belgium) where there is sex education in the schools and contraceptives are easy to obtain. 6) Providing information to teens about condom use is more likely to result in the prevention of sexually transmitted diseases among adolescents than is telling them not to have sex.

There is a curious omission in this otherwise thorough survey of sexual issues. Except for a tabular notation, masturbation is neither discussed nor indexed. Most psychiatrists regard masturbation as normal for adolescent development and a necessary and important outlet for the control and integration of the sexual drive.

Although it took almost 5 years for the content of the conference to appear in book form, the data are still relevant. There is less attention to AIDS than one might expect if such a conference were to be held today—adolescent girls and boys are now the fastest growing AIDS subgroup in the United States. However, the information about premarital sex, contraception use, age at first coitus, and the role of social pressure on sexual behavior in adolescence is applicable and useful for those who work with persons at risk for AIDS. The consensus appears to be that sex education and condom distribution in the schools are the primary means of combating AIDS, and there is the implicit recommendation that this policy be implemented nationwide without further delay.

This book is so heavily weighted toward sexual issues and reproduction that one might get the impression after reading it that adolescents are driven solely by their raging hormones. As Jean Piaget noted, adolescents are also driven by their concerns for humanitarian issues, religion, ethics, creativity, and abstractions and by their unbounded need to understand the world and their place in it. This is not meant as criticism, however, because the book does not intend to deal with those aspects of the adolescent experience. Rather, it is organized to provide an overview of adolescent sexual behavior and accomplishes that task very well. I highly recommend it to psychiatrists, psychologists, social workers, general physicians, and other workers who provide sex education or counseling to adolescents.

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**Intimate Communications: Erotics and the Study of Culture,** *by Gilbert Herdt and Robert J. Stoller. New York, Columbia University Press, 1990, 458 pp., $40.00.*

The Sambia are a small group of about 2,300 in the highlands of New Guinea who value semen very highly. ("Sambia" is a pseudonym used to protect the identity of the group.) Males pass from an exclusively homosexual behavioral period during which they swallow a lot of semen to a briefer bisexual period and, finally, to exclusive heterosexual relationships. "Semen acquisition is an imperative organizing principle of people's social interaction and sexual behavior. Its magical power does things to people, changing and rearranging them as if it were a generator." *Intimate Communications* is a book about semen and about fellatio, orgasm, masculinity, and femininity. As such it might appeal to cultural psychiatrists, a few outré psychoanalysts, and other connoisseurs of the odd. It also is a book about the acquisition, interpretation, and reporting of behavioral data. As such it may be one of the most important books of the past quarter century.

All psychiatrists have been exposed at some time during their education from college onward to that peculiarly anthropological form of study known as ethnography. Perhaps the best-known work of this genre is Bronislaw Malinowski's irrepressible *Sex and Repression in Savage Society* (1). What is striking about this form of inquiry is the contextual anonymity of the ethnographer.

*Intimate Communications* is a truly revolutionary book in which the authors examine their dissatisfactions with traditional ethnographic discourse. They ask how one can judge an individual's actual perceptions without knowing that individual. Anthropologists often tell us about the strange customs and cultures of exotic peoples, but they fail to consider the whole person as a source of intrapsychic and interpersonal meanings. Moreover, ethnographers never expose themselves, and it is an unseen hand of Science that seems to author their texts. What really happens during field work? Does not the ethnographer's personal or cultural status influence perceptions? And what about the relationship between ethnographers and their informants? Exactly what questions are asked of informants, and what answers are given?

In the 1970s Gilbert Herdt, then a graduate student in anthropology, conducted field work among the Sambia of Papua New Guinea. In 1979, Robert Stoller, a psychoanalyst at the University of California, Los Angeles, visited the field site. *Intimate Communications* is a meticulously detailed, blow-by-blow account of what transpired during interviews with informants. Although the subject matter of the interviews deals with erotics, the book is primarily about the importance of using psychiatric/psychoanalytic techniques to delineate the subjective core of ethnography. "At its center are two principles: the way researchers experience themselves is a vital ingredient of their findings; and, equally, the way informants—subjects, patients, friends—experience themselves shapes what they communicate to us" (p. ix). The result is a new form of discourse, the clinical ethnography, in which the feelings, beliefs, and motives of all the actors are described, interpreted, and compared. The process under examination begins with Herdt's first thoughts about working with the Sambia and ends with a description of the hows and whys of the editing of the book. Thus, the reader is treated to transcriptions of interviews as well to the authors' comments about their own and each other's actions. It is unlike any other book I have ever read.

*Intimate Communications* presents a logical case for the necessary consideration of subjectivity in behavioral sciences. The authors make no appeals to murky forces or ego-id-superego constructs but, rather, focus on the ramifications of individuals' conscious experiences of their institutions, beliefs, and attitudes and on the interplay between inner experience and public behavior. Although the immediate impact of this book will be on anthropology, it may be a harbinger of a pendulum swing in psychiatry. Psychoanalysis outsmarted itself with its overemphasis on psychological reality and hidden meanings, but phenomenology is becoming overbearing with its emphasis on facts (factoids?) and structured instruments. Data that are hard and reliable may also be soft and invalid. When behavior is regarded too subjectively, facts may turn to mush, but mush can masquerade as fact with too exclusive a focus on objectivity. *Intimate Communications* is a heady read, but one can always count on the Sambia to bring the authors to earth.

### REFERENCE

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**Perversions and Near-Perversions in Clinical Practice: New Psychoanalytic Perspectives,** *edited by Gerald I. Fogel, M.D., and Wayne A. Myers, M.D. New Haven, Conn., Yale University Press, 1991, 253 pp., $32.50.*

Like the postulated expansion and contraction of the universe following the initial big bang, psychiatry has had an oscillating interest in and regard for the scientific study of sexuality. In the first brilliant moments of Freudian conception, the vicissitudes of sexuality illuminated this vast expanse of the psychological domain. Human experience was moved by psychobiological instincts, and psychopathology reflected derailments in or conflicts between these erotic forces. Over time and for a variety of not fully appreciated reasons, drive theory began to sputter; concomitantly, competing psychologies of the ego, the self, and object relations developed and came to overshadow their progenitor. With the formal burial of metapsychology and its instinctual creations over the past two decades, interest in sexual experience has shrunk into a state of cold death.

It is in this context that the stirring of new work in the field of sexuality can be appreciated. *Perversions and Near-Perversions in Clinical Practice* represents a fledgling effort in this important area that has been dormant for too long.

It is unfortunate but not surprising that this reawakening requires something as scintillating as perversions to rekindle our interest in the erotic. Perversions are fascinating phenomena, worthy of serious research and study.

This book is a collection of papers, most of which were presented at a conference of the Association for Psychoanalytic Medicine in 1989. Bringing together the likes of Robert Stoller, Arnold Cooper, Louise Kaplan, Otto Kernberg, Jacob Arlow, and Joyce McDougall, Fogel and Myers have succeeded in assembling the major scholars in this field for this work. As such, it gives an excellent survey of the current psychoanalytic thinking about perversions. Unlike other conference-generated works, the chapters here are distinctive yet complementary and the book succeeds in being more than simply the sum of its component parts. Something else: it is fun to read; overall the writing is elegant and captivating.

In reading this book, one quickly notes that there are a handful of shared questions which each author attempts to address and resolve. These uncertainties involve the appropriate definition of perversions, in what manner perversity is related to nonperverse mental functioning, and how transformations can occur between sexual longings and nonsexual functioning (e.g., anxiety, character traits, and patterns of object relations).

Although there is much controversy about the defining characteristics of perversions, the contributors are just about unanimous about the inadequacy of identifying or classifying these phenomena on the basis of manifest behavior. Given an analytic crowd of authors this is not surprising. Stoller and McDougall are clearly the most vocal critics of attempts to "syndromize" perverse actions, condemning such efforts as morally based value judgments that are scientifically indefensible.

Disagreements emerge in attempts to capture the dynamic essence of perversions. Despite nuances of opinion, Cooper, Stoller, and McDougall are all impressed by the repetitive efforts to defend against and repair early (usually preoedipal) trauma. Cooper emphasizes the dehumanizing fantasies used to undo the trauma. Stoller stresses the hate that permeates the erotic script. McDougall highlights the adaptive, relationship-seeking value of perverse action.

In contrast to this consensus, Kernberg sees the hallmark of perversions in what is missing: these people are unable to engage in "the normal range of sexual experience." Using more of a self psychology model, Sheldon Bach also emphasizes signal deficits in symbolic capacity and the capacity for interpersonal involvement. Kaplan concludes that perversions represent conflicts over masculine and feminine identifications and are thus a pathology of gender role identity.

The boundary between the perverse and the nonperverse is a less contentious issue. In keeping with a dynamic framework, most of the authors see perverse mechanisms spanning a continuum from their sublimated use in creativity and play, through episodic nonobligatory sexual fantasies, to routinized enactments that are repeated ad infinitum. The only dissenting opinion is that of Helen Meyers, who asks why some individuals act out their perverse fantasies and others do not. In a brilliant chapter entitled "Perversion in Fantasy and Furtive Enactments," she argues that perversion in fantasy is qualitatively distinct from perversion in action. She then reviews possible psychostructural and conflict-based differences that may explain why one imagines and another acts. The chapter concludes with the advancement of a category of intermediate or furtive enactments between the contained thought and the all-out action.

The question of how preoedipal anxieties can be transformed into conscious sexual urges and how once-conscious sexual longings can be converted into character traits or relational patterns is not so much debated as it is serially voiced throughout the work. In my opinion, answering this question stands as the single most important challenge facing researchers in this field.

Beyond the theoretical controversy that energizes this work, there are rich clinical vignettes presented by Bach, Meyers, and Myers. Although he addresses an admirable topic, Kernberg's chapter "Aggression and Love in the Relationship of the Couple" is burdened by jargon and stereotypes. The last two chapters present analyses of perversion in literary works. In her probing study of the Greek tragedy *The Bacchae,* Ellen Handler Spitz discerns perversion as the near-universal attempt to master paradoxes inherent in the human condition through the use of splitting and doubling. George Stade brings up the rear with a riotously witty dissection of a Mickey Spillane novel that underlines the reciprocal relationship between sexual deviancy and the "straight" world of private detective Mike Hammer.

This is an important work. It will inform newcomers as well as those more experienced with psychosexual disorders. In that it addresses the relationship between sexuality and psychopathology it can be recommended for the larger audience of dynamic clinicians as well. I hope that more works of this kind will follow and that the subject of sexuality will once again captivate our field.

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**Male Sexual Health,** *by Richard F. Spark, M.D. New York, Consumer Reports Books, 1991, 230 pp., $19.95.*

We psychiatrists talk about, think about, and theorize about sexual desire a lot. So does everyone else. That is because sex is a great (arguably the greatest) shaper of individual lives, civilizations, and species. But psychiatrists have long taken a somewhat proprietary view of sexual feeling and action and particularly in the breakdown of that progression. We staked our claim early in this century. From Freud on there has been a general belief among sex therapists of all persuasions that sexual dysfunction in adults arises from mischief by the unconscious, from the snare laid early by the oedipal configuration. Certainly as late as 1980 there was general consensus among psychiatrists that, for example, male sexual dysfunction was "psychogenic" more than 90% of the time. Before that, we psychiatrists knew all we needed to know about sex, or thought we did. We thought that, in the ideal case, given enough time and a fortunate therapeutic alliance, we could find out and help the individual toward healthier libidinal expression. We gave little thought to vascular, neurogenic, hormonal, or medical/surgical causes. The majority of "sex therapists," most of whom are not psychiatrists, still deliver counseling and therapies with only vague awareness of any causality other than the psychogenic. Most treatment from mental health counselors applies behavioral techniques designed to erase inhibition, hesitation, or too much speed, with little or no regard to physical etiology.

There has been a rapid medicalization of psychiatric training, however, and we have learned more about the physical causes leading to disturbances in male sexual functioning. In addition, the aging population keeps generally healthier by use of medications and surgery, which can reduce libido or the sturdiness of an erection for men of any age. The male population that is growing older is better educated and more likely to get information from popular sources on the formerly most taboo subject. If psychiatrists are *really* to know all about sex they now need help from the outside.

Such important and timely information is available in this book. This volume is one of a series published by Consumer Reports Books, a publishing company with an obvious relationship to the monthly *Consumer Reports,* a magazine devoted to information on available consumer goods. (The idea of "consumer" has taken on broad meanings over time; the "consumed" includes services like loans, insurance, and, for many of us regretfully, medical information and care.) The dispensing of relevant information undeniably has great utility for the patient and the physician.

This book is meant for a mixed audience of intelligent lay and professional readers. The writing is diffuse for the first 50 pages or so with the intention, I assume, of providing the beginner a slow immersion. The more knowledgeable medically trained reader could simply skip these prefatory comments. With chapter 6 there begins a current, simple, clear, and useful description of the neurogenic, vascular, and hormonal factors necessary for potency and the interference with such processes by iatrogenic factors. The chapter on psychological factors serves mainly to remind the reader that although the book's primary focus is on exposition of physiological forces, the conceptually separable factors of psychogenic cause are of great importance. The book goes on to discuss the use and types of penile implants, penile injection, and hormonal pathophysiologies and treatment.

The book presents facts that may have drifted out of focus for the now presbyopic psychiatric practitioner. Those who have some uncertainty in answering the following questions, randomly extracted from the information in *Male Sexual Health,* might benefit from reading this book: 1) What is the relationship of thyroid hormone levels to male erection? 2) Does testosterone always help impotent men? 3) What is the "pelvic steal syndrome" and its relationship to potency? 4) Does prolactin (necessary for milk production) have significance for erection? 5) What is the usefulness in the treatment of impotence of a vacuum constrictor device, yohimbine, vitamin E, phentolamine, papaverine, and zinc? 6) What is the relationship of luteinizing hormone, follicle-stimulating hormone, and gonadotropin-releasing factor to potency and to fertility? and 7) Do these questions have practical clinical relevance?

There may be many clinicians who have complete clarity with regard to such questions. For many others, including myself, whose residency many years ago was mainly devoted to the constantly fascinating and elusive issues of psychodynamics, there is the suspicion that in not knowing enough about the biology of male sexual health I missed important physiological factors over the years—both in patients in treatment and in referrals. Sexual histories must certainly include psychosocial and developmental questions and must now move on to comprehension regarding aging and its impact on hormones, vascular changes, and the differential effects of medication and surgery. This book is a good way to start to come up to speed on these subjects. There is a good set of current references as an additional source of detailed information.

The second edition of this book could use somewhat better illustrations, more diagrams or flow charts (for example, of the hormonal relationships), and a bit tighter editing, particularly in the beginning. These are minor criticisms; psychiatrists and those nonphysicians who practice sex therapies would do well to read this book. Some might be embarrassed if their patients did and they did not.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Cognitive Impairment After ECT in Patients With Parkinson's Disease and Psychiatric Illness

SIR: Psychiatric illness in patients with Parkinson's disease is well documented (1, 2). Clinical depression alone is present in approximately 40% of these patients (1, 3, 4). The beneficial effects of ECT on affective and motor symptoms in patients with Parkinson's disease have been noted (2, 5). However, the indications for ECT and its potential adverse effects in patients with this disease are not clear.

We reviewed the medical records of 11 patients (six men and five women) with Parkinson's disease who received ECT for psychiatric illness between 1988 and 1990. They were 52–82 years old (mean=70 years). The diagnosis of Parkinson's disease was made by a neurologist. The duration of the movement disorder was from 1 month to 20 years (mean=5.5 years). Eight patients were taking L-dopa and carbidopa, one was taking trihexyphenidyl, one did not require treatment for mild tremor and bradykinesia, and one refused to take any medication. Also, one patient had received an autologous adrenal medullary transplant for Parkinson's disease. On the basis of *DSM-III-R* criteria, major depression was diagnosed in five patients, major depression with psychotic features in four, depression not otherwise specified and organic hallucinosis in one, and bipolar disorder with manic psychosis symptoms in one. Cognitive deficits were identified in three patients on testing with the WAIS-R, the Wechsler Memory Scale, the Auditory-Verbal Learning Test, and the Wisconsin Card Sorting Test.

All of the patients received three to nine ECTs (mean=5.9) with a Thymatron machine that delivered a pulsed, bidirectional, square-wave stimulus. The electrode placement was unilateral for nine patients, bilateral for one, and initially unilateral and then bilateral for one. Post-ECT delirium complicated the treatment in seven patients and was the major factor in the discontinuation of ECT for six of them. Of the seven patients with post-ECT delirium, five were psychotic and two were cognitively impaired and psychotic before ECT. The post-ECT delirium did not last more than 2 weeks. There were no other medical complications of ECT.

After ECT, there was marked relief from the psychiatric symptoms in three patients and some relief in six. There was no symptomatic change in two patients. Movement symptoms did not change significantly except in two patients: a transient (<6 weeks) decrease in the tremor of one patient and sufficient improvement for decrease in the dose of L-dopa and carbidopa for the other.

Our results support previous reports on the safety and efficacy of using ECT to treat psychiatric symptoms in patients with Parkinson's disease. However, the high incidence of post-ECT delirium that required early termination of treatment raises the possibility of a particular vulnerability to the cognitive side effects of ECT in patients with Parkinson's disease, especially ones with pure cognitive impairment or psychosis or both. Despite this apparent vulnerability, the majority of our patients received beneficial effects from ECT.

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## Brief Anabolic Steroid Use and Sustained Behavioral Reaction

SIR: The use of anabolic steroids to enhance the strength, performance, and appearance of athletes continues despite public reports of the destructive properties of these agents. These drugs are widely used in adolescent populations; one study estimated that 7% of male students in the 12th grade had used steroids (1). Common behavioral change in steroid users has included depression, paranoia, obsessional thinking, euphoria, and irritability (2, 3). Clinical reports that have cited these effects have noted that the athletes had used steroids for extended periods, had "stacked" several steroids together, and had used high doses. Casual steroid users may thus consider themselves not at high risk for adverse reactions. I report a case in which brief exposure to a low dose of an anabolic steroid heralded a significant detrimental change in behavior that culminated in armed robbery.

Mr. A, 20 years old, had recently graduated from high school. His premorbid personality, described independently by multiple sources, was "easygoing, polite, with exemplary social behavior." He did not abuse alcohol or other psychoactive drugs. He even volunteered as a lay counselor for delinquent youth.

Mr. A tried out for a semiprofessional football team but fell short of their minimum weight requirement. To increase his weight quickly, he took a 5-week cycle of Equipoise, beginning at 1/2 cc (4 days a week) and increasing 1/2 cc per week. He recalled becoming depressed and irritable. Family and friends, who were unaware of his steroid use, independently noted these changes. He experienced several violent rages during which he destroyed property and once became so angry that he lost consciousness. These changes continued for months after his injections ceased.

Mr. A's behavior became irrational and unpredictable. He was caught racing his motorcycle at speeds up to 160 km per hour. He decided to rob a department store where he had previously worked and disguised himself in army fatigues and a mask. After taking money while holding a nonfunctional pellet pistol, he left the store and waited outside. The police arrived, and when he was caught after a chase on foot, he challenged the officer to shoot him. Clinical examination as well as the MMPI-2 several weeks later revealed no signs of mental pathology. His IQ was in the high normal range.

At trial Mr. A received a 1-year jail sentence, much reduced from the starting point of 3 years in this jurisdiction. The judge ruled that the use of a steroid was a significant mitigating factor and that the use of this agent was distinguished from drugs abused for recreational purposes.

This case illustrates that steroids, even in limited quantities, may induce or perhaps precipitate change in behavior that continues past the period of use. In this patient, who had no prior mental disturbance, use of a steroid was correlated with an unstable emotional plane, bizarre and irrational ideas, and heightened self-confidence. The potential population at risk for steroid-related behavioral reaction may be much broader than bodybuilders and professional athletes.

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### Development of Transient Obsessive-Compulsive Symptoms During Treatment With Clozapine

SIR: I present the following two cases because of the interesting and unusual phenomenon that occurred during the course of treatment with clozapine.

Mr. A was a 24-year-old man with a 6-year history of schizophrenia, chronic undifferentiated type. He had not responded to all of the conventional antipsychotic medications. He responded favorably to clozapine, with a 35% drop in his score on the Brief Psychiatric Rating Scale (BPRS) after 12 weeks of treatment.

After he had had about 8–10 weeks of treatment with clozapine, the nurses and therapy aides noticed that Mr. A was checking his belongings over and over again. He was also checking his bedroom door, repeatedly making sure that it was closed properly before going to sleep. His own explanation of these behaviors was, "I know it's crazy, but I can't help it. I have to do it." These symptoms did not cause any significant disruption in his daily routines, and over the next 3 weeks, the symptoms gradually subsided.

Mr. B was a 34-year-old man who had a 15-year history of treatment with very high doses of various antipsychotic medications but continued to remain significantly psychotic, with various positive symptoms as well as dominant negative symptoms. Twelve weeks after he began treatment with clozapine, his BPRS score dropped by 25%.

During the 12th to the 13th week of treatment with clozapine, Mr. B developed an obsession that he was being contaminated with bacteria. He would avoid touching doorknobs and was very skeptical about touching almost anything. He would wash his hands 15 to 20 times a day and spray disinfectant all over his room several times a day. While he seemed to understand the irrationality of this behavior, he could not be talked out of doing these things. The behavior lasted about 1 to 1 1/2 weeks and subsided spontaneously.

Neither of these two patients had any prior history of obsessive-compulsive symptoms. If these symptoms occurred as a result of treatment with clozapine, it would lead to some very interesting speculations about the psychopharmacology of clozapine.

The serotonergic medications such as clomipramine and fluoxetine are very effective in the treatment of obsessive-compulsive disorders. Clozapine is a potent antagonist of serotonin receptors, and pharmacologically it would make sense if blocking off the serotonergic receptors resulted in development of obsessive-compulsive symptoms.

Perhaps etiologically schizophrenia has several subsets and one of them represents a serotonergic neurotransmitter system in the brain where too little serotonin causes obsessive-compulsive symptoms and too much serotonin causes schizophrenic symptoms. It is possible that the primary mechanism of action of clozapine is its antiserotonergic property rather than the token dopamine-blocking activity it exhibits. It is also possible that the 30% of treatment-resistant patients who respond favorably to clozapine represent this subset of schizophrenia. If so, a much less expensive and much less toxic medication such as cyproheptadine, which is also a serotonin antagonist, might play a major role in the treatment of treatment-resistant schizophrenic patients.

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### Clozapine-Induced Priapism

SIR: Priapism in patients taking clozapine has not been previously recorded. (The Food and Drug Administration has informed us that they have received three more reports of this problem since our original documentation of this case.) Priapism is defined as a persistent erection, which may be painful but is unrelated to any sexual arousal. Priapism of 4 hours' duration should be considered a urologic emergency.

A variety of drugs have become associated with priapism (1), for example, antipsychotics (thioridazine [2]), antidepressants (trazodone [3], phenelzine [4]), and antihypertensives (prazosin [5]). Various physiologic mechanisms for priapism have been described and may include increased blood flow, decreased outflow, intracorporeal thrombosis, malignant infiltrative processes, or release of cortical inhibition. In addition, it appears that acetylcholine and serotonin may be involved.

Mr. A had been admitted to a residential center at the age of 17 with a diagnosis of profound mental retardation associated with chronic auditory hallucinations. He had been treated for meningococcal meningitis at the age of 6 1/2 months and pneumonia when he was 2 years old. At age 4 he was diagnosed as profoundly mentally retarded, without any focal signs. Prior to his admission to the center, he had taken therapeutic doses of thioridazine, chlorpromazine, fluphenazine, and haloperidol. Despite numerous antipsychotic regimens, he continued to have chronic auditory hallucinations.

Clozapine treatment was started in 1990, when Mr. A was 33 years old, in accordance with a then-published protocol of the Sandoz Company. He was maintained on a regimen of haloperidol, 20 mg/day, in addition to the clozapine. On the 23rd day of the protocol, he was referred for evaluation of fever, rapid heart rate, and elevated blood pressure. A physical examination at the time revealed a blood pressure of 130/80 mm Hg, a pulse of 120 bpm, and an oral temperature of 103 °F. The single significant physical finding was a moderately infected pharynx, without exudate or regional adenopathy. As a urinalysis was requested, his caretaker offhandedly reported that Mr. A had had a persistent penile erection for the previous 48 hours. This finding was confirmed, and the Sandoz Company was notified. They informed us that as of Sept. 28, 1990, there had been no report of priapism associated with the use of clozapine. The patient was referred to the urologic service of a hospital.

In the emergency room at the hospital, Mr. A experienced extreme pain from his erection. He received repeated injections of epinephrine intracorporeally, with transient periods of resolution. A penile cutdown was performed for improved drainage of the corpora cavernosa. A Foley catheter was placed in the bladder, and the patient was admitted to the hospital for observation. Over the following 8 hours, the erection remained despite additional injections of epinephrine. Surgical intervention was then undertaken with a distal corporospongiosal shunt. The patient made an uneventful recovery from this procedure. His penis remained turgid secondary to early fibrosis.

Over the 2 1/2 months of follow-up to date, it has not been documented that this patient is able to develop an erection, which is not unexpected, since it is estimated that about 50% of patients with priapism will become impotent. Following surgery, Mr. A was restarted on haloperidol, 10 mg b.i.d. He continues to have auditory hallucinations.

A review of the literature for drug-related priapism reveals 15 different citations. Clozapine is an atypical antipsychotic without extrapyramidal adverse effects. Its frequent side effects may include hypotension, dizziness, salivation, and sedation. Agranulocytosis is an infrequent but serious side effect. As a precaution, the present protocol of the Sandoz Company requires a weekly blood level determination. Priapism should be added to the list of possible serious side effects.

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## Control of Depression With Fluoxetine and Antiseizure Medication in a Brain-Injured Patient

SIR: We have previously reported on the incidence of seizures secondary to the administration of tricyclic antidepressants in patients with brain injuries (1). Because depression can be a frequently disabling problem in this population and often requires drug treatment, nontricyclic drugs such as fluoxetine are increasingly utilized (2). Despite widespread use of fluoxetine, there is little information about the drug's effect on seizure threshold, so it is often considered to be a safe alternative to tricyclics in this regard (3). We report our first case of a possible fluoxetine-precipitated seizure.

Mr. A was a 23-year-old man who had suffered a traumatic brain injury in a motorcycle accident at age 21. He had no history of seizures either before or after his injury. Approximately 30 months after the injury, desipramine was started because of suspected depression. After 2 weeks of desipramine treatment, the patient developed two episodes of generalized seizure activity. The dose of desipramine had been increased to 150 mg/day 1 week before his seizures. The seizures were treated acutely, and the patient was given loading doses of phenytoin. Desipramine was discontinued, since it was suspected as a causative factor for the seizures, and subsequently phenytoin was also discontinued.

Since Mr. A demonstrated improved mood when taking desipramine, and his mood clearly worsened when he stopped taking the drug, a trial of fluoxetine, 20 mg/day, was initiated approximately 2 weeks after the seizure activity. Three weeks after starting fluoxetine, the patient suffered a series of generalized tonic-clonic seizures. He was acutely treated and loading doses of phenytoin were again given. Because his response to fluoxetine had been very positive in terms of mood and participation, the drug was continued along with concurrent anticonvulsant drug treatment, and he experienced no further seizures.

Although it is possible that this patient developed "late" posttraumatic seizures 2 1/2 years after his injury, it is more likely that antidepressant drug treatment, initially with desipramine and later with fluoxetine, lowered his threshold for seizure occurrence. Unfortunately, it is difficult to predict which patients may develop seizures secondary to antidepressant drugs. Fluoxetine may still be less likely to lower seizure threshold than tricyclics, but this impression could be due to a lack of aggregate long-term experience with the drug. Nevertheless, it does appear that in some cases, antidepressant treatment may be maintained when combined with anticonvulsant drugs, as has been demonstrated thus far in this case.

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## Automobile Driving by Psychiatric Patients

SIR: Recently I was involved as an expert witness in a malpractice case. A patient with schizophrenia seriously injured two persons when, with his car seemingly out of control, he struck their automobile from behind. A psychiatrist was being sued for malpractice on the grounds, among other things, that he had not advised against driving when specifically asked.

In reviewing five general textbooks of psychiatry, published between 1987 and 1991, I found no mention of driving an automobile. An early publication (1) compared the records of 271 psychiatric patients with those of 687,228 persons in the same driving environment who were not psychiatric patients. Patients with personality disorders and psychoneuroses had higher accident rates than the comparison population. Those with schizophrenic disorders had rates similar to those of the comparison group. A recent review article (2) found no evidence that schizophrenia increased the number of road traffic accidents, either in the United States or in Denmark. Manic disorders might be potentially dangerous, but adequate data were lacking. Depression might contribute to accidents by virtue of slowed responses or suicidal intent; however, only 1.7% of fatal accidents were attributed to suicide. The clearest indication of a psychiatric disorder impairing driving involved a patient with Alzheimer's disease. Among 522 consecutive patients with dementia, 333 were licensed to drive at the time of onset of their dementia. However, the median length of time during which they drove after onset was almost 29 months. Most important, 21 of the 93 patients still driving at the time of the survey had been involved in motor vehicle accidents within the previous 6 months (3).

The absence of any guidelines in formal psychiatric texts and the paucity of the scattered literature suggest that the psychiatric profession feels little responsibility to determine fitness to drive. Such an attitude might be justified by the fact that it is really those persons closest to patients who might be most aware of their limitations. The decision about what advice to offer then becomes a matter of common sense. Some cases are easy; any lay person would be reluctant to ride in a vehicle driven by a wildly hallucinating person. The more difficult cases might be those in which the patient has attained some degree of remission. It might still be prudent to err on the side of conservatism. Operating a motor vehicle is deemed by most people as a right to be abrogated only under the most stringent circumstances. As long as psychiatric patients who might be impaired can freely obtain licenses, psychiatrists can only offer advice. In flagrant cases such advice might be volunteered. When one is asked directly, the pros and cons of driving should be discussed until some conclusion is reached. The issue can no longer be evaded.

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## Experiences in Beginning Therapy

SIR: My group of students in their second postgraduate year is currently experiencing the anxieties and rewards of beginning therapy with a variety of patients in such diverse settings as a locked unit, an open unit, an emergency service, and office visits. I have become interested in the dynamics of such first meetings and the expectations and emotions that the therapist brings into the session. I am soliciting anecdotal accounts of first encounters with patients, with the intention of publishing an anthology, tentatively entitled *At the Very Beginning.* Contributions from all disciplines are welcome. Manuscripts should be double-spaced and range in length from 2 to 20 pages.

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## "Pseudohypermnesia": A Conscious Effort to Avoid Telling the Truth

SIR: A felon endlessly added new details to his allegations. He insisted that no one could ever know the whole story and that until the whole story was known he could never be found guilty. The added facts were, by and large, impossible to verify. His presentation gave the clear feeling of confabulation, but it was not an unconscious filling in with imagined or untrue experiences; rather, it was an obvious and designed behavior.

We propose the term "pseudohypermnesia" to describe this phenomenon of intentionally and consciously exaggerating the degree of retention and recall. It is meant to be different from paramnesia (falsification of memory by distortion of recall) or retrospective falsification (adding false memories to true memory) because the added memories may not be entirely false but just detractors. In pseudohypermnesia the memories may or may not be true, and the pseudohypermnesic person will not resist efforts to verify his story; his willingness is partially based on his assumption that we do not have the time, interest, or energy to make such an investigation. Furthermore, he knows that witnesses cannot be located, and so his story remains free from attack. And ultimately he can always add another variable.

This is not the memory equivalent of a neologism. The memories are not necessarily created by the person, although there may be some effort at retrospective data forgery to fortify his allegations.

Obviously, this reflects deficits in insight, but it is not automatically an impaired judgment, because such behavior has probably worked in prior situations and so has reinforced itself. It does contain some narcissistic and antisocial personality qualities.

Studies of hypermnesia suggest that memory and recall are both vulnerable to the person's understanding of the consequences of his recall (1–5). Recall can even be faked on formal neuropsychological testing. Hypnosis offers no significant increase in valid recall; it appears limited to widening the person's criteria for what he declares to be a valid memory. There is some question about the order of testing and interviewing. Rey's test for malingering may have more clinical value if it is used before other testing and interviewing occurs, so subjects are not sensitized to its intent. On the other hand, there is evidence that repeated attempts at recall with eyewitnesses to events may foster accurate hypermnesia; the difference between hypermnesia and pseudohypermnesia is that the additional memories in the former increase the accuracy of recall, whereas in the latter, repeated efforts at questioning the subject may provide a greater chance that credibility will be further diluted.

In summary, we propose the term "pseudohypermnesia" to mean an unbelievable and extraordinary amount of "precise" recall, with an endless list of possible details, excuses, and variables with respect to why or how an event occurred. Usually, pseudohypermnesia occurs when the person wants to mislead the listener.

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### Sequelae of Denied Abortion

SIR: "The Psychological Sequelae of Therapeutic Abortion—Denied and Completed" by Paul K.B. Dagg, M.D. (1) is excellent. We would like to underline the sequelae of denied abortion, as political and public attention to this issue continues to increase. We were struck by the cases of two patients who recently came to our small general psychiatry inpatient unit in a state hospital facility within just 1 month's time.

Ms. A, a 23-year-old single woman who abused cocaine and heroin, was sent involuntarily to the state hospital from a general hospital that did not have a psychiatric unit. She had presented to the hospital "binging on cocaine for a month trying to kill the baby" and saying she would kill herself if she did not get an abortion. The abortion was performed, and the patient was sent to our hospital for further evaluation. She denied having had psychiatric treatment or formal detoxification in the past and denied ever being suicidal, saying she had only threatened suicide to obtain the abortion. She also denied being depressed. At the end of a week's hospitalization, after further history had been obtained from her family, her boyfriend, and the previous hospital, it was determined that she was not then a danger to herself or others and, at her insistence, she was discharged to outpatient counseling, Narcotics Anonymous, and gynecologic follow-up.

Ms. B, a 28-year-old divorced woman, was transferred involuntarily on physicians' certificates from a local hospital emergency room. She said she would hurt herself or get her boyfriend (not the father of the fetus) drunk so he would beat her up, in an attempt to kill the fetus. She worried that the Department of Social Services would not process her "paperwork" in time for her to obtain a legal abortion. She reported no past psychiatric hospitalizations. She noted that she already had two young sons and was in a custody battle with her parents over them. She also cited severe back pain, getting a new job, and moving in with her new boyfriend as other reasons for wanting an abortion. She insisted that a baby would "ruin" her life. She felt that no one was willing to help. The patient soon began denying thoughts of hurting herself, saying she wanted to leave and take care of her problems. She was released by an administrative law judge in a hearing after 4 days. Her social services worker was contacted, and an outpatient clinic appointment was made.

Such cases humanize the abortion discussion. We support APA's strong prochoice position that "any decision on abortion should be strictly between a woman and her physician" (2). A woman who desperately wants an abortion will get one. Some 40% of women who are denied abortions receive them elsewhere (1). Dr. Dagg also describes as "alarming" reported rates of "spontaneous" abortion in this population, when spontaneous miscarriage should be rare. We are again concerned that restrictive legislation on this issue, as on others, most affects those who are already disadvantaged, those who already have fewer choices. Last, but by no means least, we were struck by the findings that few children of unwanted pregnancies are adopted out, and the remaining children suffer "long-lasting, broadly based, negative effects." We are gravely concerned for the children of unwanted pregnancies and grimly expect to see them in our clinics and hospitals through the years.

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### Factors Affecting Patient Dropout Rates

SIR: The study on patient dropout rates by William H. Sledge, M.D., and colleagues (1) warrants comment because of methodological problems and the possible misuse of their conclusions by regulators pursuing fiscal restriction in psychiatric practice. The authors' results would appear to support the hypothesis that time-limited psychotherapy has the intrinsic advantage of a lower dropout rate than approaches lacking a pre-set termination date, suggesting greater cost-effectiveness without regard to patient selection and outcome measures.

Several easily measured variables not mentioned in the report that could have accounted for the differential dropout rates include 1) length of the assessment phase preceding referral, 2) dropout rates during or after assessment but before starting treatment, 3) transfers to a different clinician for treatment after the assessment, 4) frequency (as opposed to length) of therapy, 5) the therapist's professional discipline, 6) type of sex pairing, and 7) prior dropout history. Differential outcome measures, such as recidivism rates, are also relevant. In the literature on treatment dropouts there is evidence to suggest that an evaluation phase of more than one session tends to decrease the likelihood of dropping out of treatment (2), transferring patients to new clinicians for therapy increases the likelihood of dropouts (3), higher frequency of sessions is associated with remaining in treatment (4), professional affiliation and sex matching can be related to therapist "holding power" (4), and previous dropouts from treatment are more likely to drop out again (5).

If, for example, patients selected for time-limited psychotherapy in the study by Dr. Sledge and associates happened to have a longer evaluation phase than the other groups (say, in order to determine suitability, assess motivation, and set a focus), it is possible not only that an extended evaluation increased the likelihood of their staying in treatment but also that any attrition was more likely to have occurred before treatment began. Independent of diagnosis, patients selected for time-limited psychotherapy might have been considered more suitable, motivated, or attractive therapy candidates who made better matches and thus may have been less likely to be transferred to another clinician after assessment. (Differential transfer rates provide a window on the issue of selection bias. Selection factors are critical, as illustrated in the review by Reder and Tyson, cited by Dr. Sledge and associates, in which patients in brief psychotherapy had a lower dropout rate than patients in long-term psychotherapy, but the lowest dropout rate was among patients in psychoanalytic treatment.) In addition, the brief psychotherapy patients on average had fewer sessions than the time-limited psychotherapy patients, suggesting that the latter did, in fact, meet more frequently.

It is noteworthy that some of the therapists in the study were in a didactic seminar on the time-limited method, which was being taught and developed as the clinic standard for brief psychotherapy. A "halo effect" would have been difficult to avoid. By analogy, patients have been known to dream more when their therapists participate in a dream seminar, even though this fact is not voiced to the patients, who become "better patients" by dreaming more, perhaps because dream material is elicited more or because of other, nonverbal cues from the freshly interested therapists.

While the conclusions of Dr. Sledge and associates may still be corroborated upon a fuller consideration of variables, the scientific and therapeutic basis for recommending a time-limited approach over other therapies for patients in general has not been clearly established. This point is worth emphasizing at a time when, as in Massachusetts, some public policy makers, regulators, and insurers seek to restrict the range of treatment options.

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## Dr. Sledge and Associates Reply

Sir: Dr. Good's letter addresses some important considerations. We examined some of the suggested and alternative hypotheses that he mentions before we wrote our report, and we will simply say what we can about them at this point. 1) There was no difference in the length of the assessment phase or the number of assessment interviews between dropouts and those who remained or among the three different types of psychotherapy reported in our article. 2) Patients who dropped out before treatment began were not included in our report. 3) There was no difference among the three types of treatment and the transfer to a different clinician from the evaluating clinician, and there was no statistically significant difference between dropouts and those who remained on transfer from a different evaluating clinician. 4) We did not analyze the frequency of therapy because almost every treatment involved weekly sessions only. 5) As noted in the article, there were no statistically significant differences in the professional disciplines of therapists by type of therapy. 6) We did not examine the type of sex pairing. It is certainly a reasonable and interesting hypothesis, but differences in both same and different sex pairs could not account for the robustness of our finding. 7) We do not have data to address the point on prior dropout history. However, it should be remembered that the patients were relatively new to psychiatric treatment, and all had been out of the clinic in the 2 years before the study. Again, it is highly unlikely that prior dropout history could account for the robust findings we reported.

Dr. Good makes the point that there could be a halo effect secondary to the acquisition of a new skill and knowledge from an enthusiastic staff. This is a possibility; and, of course, it is the reason we indicated in the article that some staff members had recently learned the Mann method. But many staff members also were learning to do brief treatment not based on Mann's technique. However, as we reported, brief treatment without the Mann technique had twice the dropout rate of brief treatment with the Mann technique. Dr. Good also notes the possibility of a selection bias. We think that it is indeed possible that some subtle selection bias occurred, but not necessarily along the lines he suggests, namely, that the time-limited patients were more "suitable, motivated, or attractive therapy candidates."

As indicated in the article, our study was archival and retrospective and, therefore, subject to the possible influence of uncontrolled biases. Given that fact, it would be highly inappropriate for policies of a public or private nature to be based exclusively on our report. On the other hand, the finding was very robust, and it would be highly inappropriate to ignore it. A useful response to the study would be to do a prospective investigation of the issues.

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## The Opioid System and the Placebo Response

Sir: We were interested in two articles published recently regarding the placebo response in patients receiving antidepressants (1, 2). The authors highlighted possible different types of placebo response, contrasting rapid improvement to a more gradual process. The latter type of placebo response has to be distinguished from spontaneous remission. The authors mentioned that the dramatic onset of abrupt and sometimes transient mood improvement suggests that some endogenous substance might be involved. Their candidate was phenylethylamine (1). It is possible that the endogenous opioid system may also be involved (3, 4). A variety of endogenous and exogenous opioid compounds have been shown to elevate mood (5). In our studies dealing with alcoholic withdrawal states (3, 4), we initially administered placebo and used an active substance only after the placebo trial had been completed. This paradigm seems to have been similar to the one used by Dr. Quitkin and associates (1).

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## Meaning of Refractory Depression

SIR: Richard Guscott, M.D., and Paul Grof, M.D., Ph.D. (1) provided an excellent review on the clinical meaning of refractory depression. They noted that "suggestive evidence points to the coexistence of a medical or nondepressive psychiatric disorder as a problem in depressed patients who are considered refractory to treatment." In fact, there is a substantial body of data indicating that persons with secondary depression are less likely to achieve recovery than persons with primary depression (2). Although the primary/secondary diagnostic scheme has never achieved popularity, it remains one of the best validated (3).

Drs. Guscott and Grof failed to note that the presence of an accompanying personality disorder also has substantial impact on response to treatment (4). It is important to point out these associations, since clinicians need to understand which variables have an impact on recovery.

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SIR: The article by Dr. Guscott and Dr. Grof was excellent. I would like to highlight and ask them for clarification of a point they made that resonated with my own clinical experience. Concerning serum monitoring of antidepressants, they noted, "There is virtually no evidence to demonstrate that the use of serum monitoring in routine clinical practice improves therapeutic outcome. We also suspect that in many clinical situations the monitoring of tricyclic antidepressant levels can lead to inappropriate clinical decisions. We have observed many situations where patients have been kept on subtherapeutic doses because of levels above the 'therapeutic' range" (p. 698).

In our center, especially of late, there seem to have been many values in the 150–250 ng/ml range with therapeutic doses of nortriptyline. The therapeutic range is reported to be 50–150 ng/ml. Concerned about laboratory error, we got a confirmatory value from a second laboratory in a recent case. Although these two values were close—175.6 and 169.0 ng/ml—they were both quite different from the value of 235.1 ng/ml reported 3 days earlier when the patient was taking the same dose, 100 mg at bedtime. The patient's ECG was normal.

Generally, I have had levels ascertained 3–4 weeks into treatment, when an optimal response has not yet been achieved, with the rationale of "seeing where things stand," especially concerning the further increase of antidepressant dosage. When the level has been greater than 150 ng/ml, I have been torn between lowering the dose (recently, in one instance I did that and the patient experienced a clinical worsening of depression) or leaving it as is (done with four patients), noting in the chart concerns about the validity of the laboratory values and the absence of clinical toxicity. I have not had the "guts" to increase the dose further in the face of an already "high" level.

Are we ascertaining antidepressant serum levels too routinely or too soon? I would appreciate the comments of Drs. Guscott and Grof.

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## Dr. Guscott Replies

SIR: Dr. Black makes two observations on our review that raise serious and challenging scientific and clinical issues. First, he points out that the category of "secondary" depression is much more validated than we have implied. Clearly, there is good evidence that patients with secondary depression have a poorer treatment response than those with "primary" depression. His own research clearly supports this position (1). His point is well made. His own research also points to inadequate treatment of secondary depression as a major clinical problem.

However, there appears to be continuing controversy about the validity of the distinction, reflected in the failure of *DSM-III-R* to recognize the distinction. We would conservatively share the view of others that the separation of primary from secondary depression, although controversial, is required for pragmatic reasons (2).

Dr. Black further states that we failed to note the substantial impact of a personality disorder on response to treatment. In fact, in our review we stated, in agreement with Dr. Black, that the "coexistence of a medical or nondepressive psychiatric disorder" is a factor in response to treatment. The extent of this impact on treatment response, we think, is unclear. The NIMH collaborative study cited by Dr. Black pointed to mixed results. The researchers' own interpretation of the results was that although patients with personality disorder had a less favorable result, this depended upon the outcome measures used. For example, there was no difference in outcome on mean Hamilton Rating Scale for Depression scores, work functioning measures, or the HSCL-90 depression scale. Social functioning was less improved in the personality disorder group. However, the log linear analyses of Personality Disorder Group by Treatment by Recovery revealed that "patients with personality disorders improved" but were "more likely to have residual symptoms of depression" (3). In our view, this means clinically that we must have good baseline measures of both symptoms and functioning, with the appropriate targeting of our interventions.

Dr. Storch raises a challenging clinical question with regard to serum antidepressant monitoring. The question of "too routinely or too soon," in our view, depends on the clinical context (and in some areas, perhaps the legal context!). Our own position is that levels themselves are only guides and do not indicate either toxicity or the "upper limit," similar to digoxin levels. Only a clinical assessment can determine toxicity. In my own practice, a high level (above the "therapeutic range") in the absence of major side effects would not be a contraindication for increasing the dose.

Although others, notably Preskorn and Jerkovich (4, 5), have made excellent arguments for the clinical use of serum monitoring, we remain concerned that some clinicians continue to treat the "levels" rather than the patient.

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## Performance Anxiety

Sir: As a professional musician and a psychiatrist frequently consulted by performing artists afflicted by stage fright, I read with interest the article on performance anxiety by Duncan B. Clark, Ph.D., M.D., and W. Stewart Agras, M.D. (1). I doubt, however, that the method used to assess the level of anxiety in the subjects adequately replicates a real-life performance experience. In addition, I wish to ask the authors what criteria they used to determine a "better" or "worse" musical performance and those for selecting the raters.

My own therapeutic approach to the problem of stage fright is eclectic and includes an insight-oriented as well as a cognitive aspect. Except for the beginning phase of treatment, where β blockers can be of real temporary help, I agree with the authors that minor tranquilizers should be avoided.

I highly recommend the reading of *The Inner Game of Music* (2), which provides a useful self-help guide to many of my patients.

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## Dr. Clark Replies

Sir: I thank Dr. Chanel for his interest in our work. With regard to the method used to assess performance anxiety, the laboratory evaluation did include a live performance experience. We believed that it was methodologically important for the performance setting to be the same for every subject, and identical before and after treatment. Therefore, it was not feasible to use performance situations that the subjects would naturally encounter outside the laboratory. In the laboratory performances before treatment, subjects reported a mean subjective anxiety level of 7.1 (range=2–10) and had a mean increase in heart rate of 31.4 bpm (SD=16.2). Informally, subjects indicated that the setting was similar to an audition or juried performance. While this was not identical to each subject's unique naturally occurring performance situations, we believe this method to be valid.

These laboratory performances were audiotaped and were presented in random order to experimentally blind raters. The raters were asked to compare two performances of the same piece by each subject without knowing which was before and which was after treatment. They then rated the second of the two performances on a scale ranging from "much worse" to "much better." When the subject was performing a classical piece, a musical score was provided to the rater. The diverse nature of the musical performances, which included a jazz drum improvisation, an original country western song with guitar, and an operatic aria, precluded the possibility of a uniformly applied objective criterion such as an error count. The raters were undergraduate music students with extensive performance experience.

While insight-oriented psychotherapy may be helpful for some musicians, this method has not been demonstrated to be useful for performance anxiety. A review of the literature (1) shows that, aside from case reports, the use of psychodynamic psychotherapy for performance anxiety in musicians has not been studied. The most relevant controlled study was on speech anxiety and showed psychodynamic psychotherapy to be equivalent to an attention placebo (2). On the other hand, our study adds to a growing body of research documenting the effectiveness of cognitive-behavior therapy for performance anxiety in musicians.

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## Factors in Homelessness Among Psychiatric Patients

Sɪʀ: In a recent article (1), Ezra S. Susser, M.D., M.P.H., and associates extended their important research (2) elucidating childhood antecedents of adult homelessness among psychiatric patients. They found an impressively high rate of foster home placement in childhood among patients in a state hospital who had ever been homeless, ranging from 17% to 22%, compared with 2% for the never-homeless patients. Less effective kin support is the mechanism the authors hypothesized as the link between foster care in childhood and adult homelessness. One could perhaps say that many of these individuals thought of themselves as homeless even in childhood, long before they became chronically mentally ill. More than two-thirds of the authors' state hospital sample, presumably equally ill, had never been homeless. Clearly, homelessness follows a complex series of events, and the presence of a serious psychiatric disorder is only one of many factors.

It has been fashionable to blame deinstitutionalization for the increase in homelessness in the 1980s, even though during the peak years of the depopulation of state mental hospitals, beginning in 1955, homelessness was not a serious problem. The theory that homelessness is caused by mental illness and mental health policy has been embraced by our field despite the lack of evidence to support such a position (3).

This view, fortunately, is gradually shifting. Increasingly, advocates for the homeless and even some mental health professionals cite multiple factors as the causes of homelessness: high unemployment, limited education and skills, the low wages of many workers, increased numbers of single-parent families, loss of family networks, disappearing low-income housing stock, a diminution in the availability and generosity of social welfare benefits, physical disabilities including AIDS, and the complex relation between substance use and all of these other stressors.

The mental health system has a role to play in addressing homelessness, but that role is limited to certain specific interventions, such as the one proposed by Dr. Susser and associates, which we have the resources and expertise to implement. We should not be too eager to claim responsibility, or accept blame, for the increasing public squalor of American life.

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## The Mind-Body Problem

Sɪʀ: Aviel Goodman, M.D., in his article on organic unity theory (1), provided a conceptual framework for psychiatry that has a basic flaw. To say that "the conventional dichotomy between physical (organic) and mental (functional) is linguistic/conceptual rather than inherent in nature" (p. 553) is to beg the question, as it sets up another dualism. A monistic stance is needed (the middle column of Dr. Goodman's figure 1) which places dualistic terms (the right-hand column) and monistic terms (the left-hand column) on a continuum, in order not to deny either, which would cause the perspective to regress to dualism.

Moreover, such terms must link dualistic and monistic terms in an asymmetric fashion. Dualistic terms establish a symmetry between opposite categories from the perspective of a supraordinate category. Monistic terms establish a continuity between opposite categories that is latently dualistic and symmetric because of its reversibility when viewed from the perspective of the supraordinate category, which is equivalent to a perspective within the continuum in which forward and backward are interchangeable. If, and only if, this continuum is asymmetric can monism be liberated from latent dualism and become a "psychophysical term," an "embodiment" of a dualistic term, or an "ensoulment" of a monistic term with dualistic subjectivity.

For example, absolute irreversibility of time (making its appearance with quantum mechanics) seems to "ensoul" physical reality. It "embodies" consciousness by asymmetrically connecting the categories of past and future, from the perspective of the present moment, wherein an ordered or timeless mode of knowing (dualism) applicable to the subjectively experienced past in contrast to the future, and a timeful, nonhierarchical mode of knowing (monism) applicable equally to all times, coincide (Richard P. Goldwater, unpublished manuscript).

All psychiatric disorders can be completely described as failures of integration of the two modes of knowing (Goldwater, unpublished manuscript). Severe lesions in categorical thinking produce schizophrenia-like syndromes, and severe lesions in monistic thought produce affective (or categorical) disorders. The neuroses can be understood as failures of integration of dualism and monism, incarnate in the child's perspective as Mom and her relationship with Dad in the Oedipus complex. Problems with "separation-individuation" are more clearly understood when separation is seen as dualistic and individuation as the monistic complement.

Both biological and psychological psychiatry share a prejudice against dualism and therefore against "events, states, and processes . . . to which both mental and physical concepts refer" (p. 558), because such things require a monism that incorporates dualism rather than a monism that perpetuates it.

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Sɪʀ: The respectable attempts to unify the mental and the physical (Carnap's theses of unified science, Feigl's identity theory, etc.) suffer distortions in the hands of Dr. Goodman. For example, he says, "Physical terms are associated with statements that are intersubjectively confirmable, whereas mental terms are associated with statements that are only subjectively confirmable" (p. 556). Compare the sharply contrasting view of Feigl (1), whom Dr. Goodman quotes approvingly: "The decision to rule out as scientifically meaningless statements which are not even indirectly confirmable . . . reflects the conviction that whatever is subjectively verifiable is in principle also intersubjectively confirmable." This is a cornerstone of "identity" philosophers' view, since they regard the language of objective science as the only meaningful language. Carnap (2) was the first to point out that there cannot be a subjective term in intersubjective language which could not be explicated behaviorally. A child learns to say "I am tired" after hearing the parents saying it because they notice behavioral signs of fatigue, or the situation calls for such an expectation.

Dr. Goodman says, "There exist 'pure psychophysical events' that the subject and the observer experience differently . . . and that they designate with different classes of concepts" (p. 557). But any scientifically respectable concept must have intersubjective criteria of application and thus be, according to Dr. Goodman, physical.

The practical consequences of Dr. Goodman's position are similar to those of dualism. He sees a possibility of formulating a psychiatric diagnostic system in physical concepts, in mental (subjective) concepts, or in a combination of the two, but the last "is likely to lead to confusion on logical as well as factual levels" (p. 562). However, the trend of psychiatry seems to be to integrate the subjective, behavioral, and neurophysiological data. That has also been the philosophical background of the attempt of one of us (F.K.) to integrate psychotherapy (3). Does not Dr. Goodman himself say, "The identity theory postulates that the referent of a mental term is identical to the referent of a corresponding physical term" (p. 557)? And Feigl concludes, "Private, immediate experience as such is only the raw material, not the real subject-matter of science."

In practice, Dr. Goodman's position leads to compartmentalization of psychological and psychiatric concepts. He criticizes Engel for talking about experience and behavior at the same time and says, "Experience is a mental concept, representing direct, first-order knowledge . . . that is confirmable only subjectively; behavior is a physical concept" (p. 558). Let us assume that a certain task cannot be successfully accomplished unless one understands and remembers the appropriate instructions. We then conclude that a person who accomplishes this task has gained that experience, without asking about that person's subjective experience. Then "experience" is a behavioral concept which can be coordinated with a subjective concept.

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SIR: Dr. Goodman presents a clear and detailed treatment of the mind-body problem that is informed by recent work in the philosophy of science and applicable to general psychiatry. His position, in summary, is 1) that the current biopsychosocial paradigm, as evolved from general systems theory, ultimately entails a dualistic account of mind-brain relationships, 2) that mental-physical (mind-body) identity theory, as developed in the philosophical literature, avoids "dualistic fallacies" (p. 561), and 3) that a synthesis of the biopsychosocial model and mental-physical identity theory resolves the mind-body problem and obviates misleading biological-psychosocial dichotomies. The argument includes a concise review of the philosophical difficulties in dualism, e.g., "if a mental force that could influence physical entities and processes were postulated, it would then by definition also be a physical force, which would not be consistent with dualism" (p. 555).

Mental-physical identity theory holds that the seemingly radical difference between the mental and the physical is an artifact of point of view and of differing conceptual systems: "the mental and the physical are not two realms or concomitant types of events but one reality represented in two conceptual systems" (p. 557). The difference is epistemological, not ontological.

Dr. Goodman argues that the standard view of a systems hierarchy can be modified to preserve the epistemological distinction between the intersubjective, neurophysiological realm and the subjective, experiential realm without requiring either reductionism or dualism. An intriguing aspect of Dr. Goodman's thesis is that mental systems may be conceptualized in levels of organization that are not restricted to those coextensive with brain activity. During interpersonal communication, for example, there clearly exists a meaning and information exchange process that is superordinate to the mental processes of a single brain. He states, "Conceptualization of this possibility—of levels of organization of mental systems other than the human nervous system—is limited by the difficulty in attributing phenomenal experience to levels of organization designated by subpersonal or suprapersonal terms and in imagining what other forms of mental properties there might be at these levels" (p. 559). Indeed, psychiatry already contains a rich store of data—from study of phenomena such as unconscious fantasy, ego psychology and object relations, transference/countertransference, group process, and family dynamics—that could guide investigation of subpersonal and suprapersonal mental properties.

I would take issue with Dr. Goodman's statement that the biopsychosocial model's provision for the mind-body problem is "flawed" (p. 553). The biopsychosocial model, through its conceptual relationship to general systems theory, may have philosophical implications but is not, strictly speaking, a philosophical theory; it is a general conceptual framework for empirical activity not designed to resolve philosophical issues such as the mind-body problem. Mental-physical identity theory, on the other hand, explicitly postulates a general, ontological account of events and reality.

Dr. Goodman's organic unity theory is indeed a "synthesis" (p. 558) of the biopsychosocial model and the more philosophical mental-physical identity theory, not a correction of a flaw in the former by use of the latter. The article stands as an example of rigorous philosophical thought being used to clarify fundamental tensions in our field and extend the horizons of research.

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## Dr. Goodman Replies

SIR: I am grateful to Drs. Jacobs, Knobloch, Hahn, and Setterberg for their interest in my article and for the thoughtful and thought-provoking feedback they have offered. The letters from Dr. Jacobs and Drs. Knobloch and Hahn have been particularly helpful in calling to my attention a flaw in the presentation of my position. Both correctly point out that redefinition of the mental-physical dichotomy as linguistic/conceptual rather than inherent in nature, while intended only to describe the culturally prevalent pattern of linguistic/conceptual practice, in effect perpetuates dualism in one form or another: either a dualism between mental reality and physical reality (if reality which is apprehended conceptually is the only reality that we consider real) or a dualism between what is apprehended conceptually as real and the reality that exists apart from our conceptual apprehensions. In the context of my formulation, the claim that "pure psychophysical events" are real would presuppose the latter form of dualism; the claim that they are not would entail the former.

Mental terms and physical terms differ in significant ways and can be segregated to form classes that reflect these differences. The linguistic/conceptual realm is, however, best represented not as two or more discrete networks but as one continuous network (1, 2). What then constitutes the difference between mental and physical areas within this network? The distinction between statements that are intersubjectively confirmable and those that are confirmable only subjectively does not withstand scrutiny, since all language is learned intersubjectively and must continue to have some degree of intersubjective confirmability in order to function as a means of communication. Intersubjective confirmability is in any case not a property of a statement in itself; it is a property of a statement in a particular context and depends on what is accepted as constituting evidence for confirmation and on the ability of the evaluator to perceive and assess that kind of evidence. At this time, my best formulation is that the difference between mental and physical terms can be characterized according to the type and complexity of the collateral information required to accept a given event as confirmatory evidence, the knowledge and abilities necessary to perceive and utilize the collateral information, and the degree of resistance to changing a judgment about whether an event constitutes confirmatory evidence (which is related to the collateral information factors). This idea parallels Mary Hesse's thesis (3, 4) that observational and theoretical terms differ only in their degree of entrenchment and the conclusion of van Brakel and Geurts (5) that literal and metaphorical meanings differ only in their degree of social fixity.

While I agree with the criticism noted in the preceding paragraphs and appreciate the stimulus to improve my formulation, there are a number of points in the letters from Dr. Jacobs and Drs. Knobloch and Hahn that I have difficulty accepting or perhaps do not correctly understand. In the first paragraph of his letter, Dr. Jacobs identifies the right-hand column in my diagram (which represents the conceptual network of mental terms) as "dualistic terms" and the left-hand column (which represents the conceptual network of physical terms) as "monistic terms." There is no explanation of why mental terms should be considered dualistic while physical terms are considered monistic. Meanwhile, this suggestion does not eliminate the linguistic mental-physical dualism that characterized my initial formulation; it merely relabels it—and with terms that seem to convey less relevant information than do the original terms. The second paragraph may express some important ideas, but I find it difficult to understand. It is not clear which terms "must link dualistic and monistic terms in an asymmetric fashion," nor is it clear how this linkage contrasts with the symmetrical relationship presumably established by dualistic terms. The final sentence is particularly confusing. How can monism at the same time be a "psychophysical term," "an 'embodiment' of a dualistic term," and "an 'ensoulment' of a monistic term with dualistic subjectivity"? Discussion in the third paragraph presupposes conceptual relationships that are not readily apparent and could benefit from clarification, as with the following questions: How are the terms "ordered" and "timeless" interchangeable in describing a mode of knowing? What is the connection between dualism and the ordered or timeless mode of knowing? How is "ordered" opposite to "absolute irreversibility of time"? (the latter phrase is more clearly in opposition to the idea of a time-space continuum, which is an aspect of relativity theory). And what is the relationship between the dualism-monism dichotomy and the timeless-time irreversibility dichotomy? The statement with which the fourth paragraph begins—"All psychiatric disorders can be completely described as failures of integration of the two modes of knowing"—is quite an ambitious claim to make without any substantiation. It neglects the physiological, behavioral, interpersonal, and psychodynamic aspects that are also involved in a complete description of psychiatric disorders, and it seems to mistake symptom for cause. The final paragraph of the letter cites part of a sentence from my article and associates it with dualism. The original sentence reads, "In between, in parentheses, are terms which represent systems of events, states, and processes (either postulated or imaginary, but in any case indemonstrable) to which both mental and physical concepts refer" (p. 558). It is clearly monistic with respect to the events, states, and processes, so the statement that a "prejudice against dualism" is "therefore against 'events, states, and processes . . . to which both mental and physical concepts refer'" does not make sense. In fact, the sentence is referring to the middle column of my diagram, which Dr. Jacobs in his first paragraph identifies with a monistic stance.

The letter from Drs. Knobloch and Hahn claims in its first paragraph that "respectable attempts to unify the mental and the physical . . . suffer distortions in the hands of Dr. Goodman" and offers as evidence statements of Feigl and Carnap which contradict my formulation of mental-physical identity theory. As I have acknowledged above, the proposition that the distinction between mental and physical terms depends on intersubjective confirmability (which I borrowed from Feigl) is incorrect. I do not agree, however, with the claim that "the only meaningful language [is] the language of objective science" or with Carnap's point that "there cannot be a subjective term in intersubjective language which could not be explicated behaviorally." Postempiricist philosophers of science have convincingly argued against both of these positions, and neither of them is presupposed or entailed by mental-physical identity theory. Philosophy of science, like science itself, develops in a historical process: as the theoretical context within a field evolves, the theoretical positions that were once taken for granted come to be questioned and on occasion are found to be flawed. The fourth paragraph contains a few minor inaccuracies. It begins with the statement that my position "leads to compartmentalization of psychological and psychiatric concepts," while my position actually describes a functional compartmentalization that is already in effect. The next sentence of the paragraph observes that I criticize "Engel for talking about experience and behavior at the same time." My criticism of Engel is not for talking about experience and behavior at the same time but for implying that they are in the same logical category and that experience is emergent relative to physiological processes. The paragraph concludes with the statement, "Then 'experience' is a behavioral concept which can be coordinated with a subjective concept." I would be willing to consider hypotheses that, within the realm of reality to which the term "experience" applies, there are behavioral concepts which correspond with subjective concepts (such hypotheses would be examples of the "hypotheses of correspondence" or "empirical identifications" to which I refer on p. 557 of my article). I would, however, apply the term "experience" to the subjective aspect of this correspondence relationship, not the behavioral. Learning and behavior theorists generally exclude "experience" from the scientific vocabulary, since it is not directly observable and has no operational definition.

Dr. Setterberg's letter presents a clear and concise review of major points in my article. I particularly appreciate his correction of my unnecessarily limited perspective regarding mental properties at subpersonal and suprapersonal levels of organization. I agree with the statement in Dr. Setterberg's closing paragraph that organic unity theory is a synthesis of the biopsychosocial model and mental-physical identity theory, not a correction of a flaw in the former by use of the latter. However, I continue to believe, for the reasons discussed in my article, that the biopsychosocial model's provision for the mind-body problem—its conceptualization of mind as emergent from brain—is flawed. My final comment on this letter concerns the claim that the biopsychosocial model is not a philosophical theory but a "general conceptual framework for empirical activity." I am not sure how distinct the boundary is between the class of philosophical theories and the class of general conceptual frameworks for empirical activity, and my sense is that the latter is a subset of the former.

Again, I thank the authors of these letters for sharing their thoughts and providing me the opportunity for further development of my own ideas.

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### When a Patient Commits Suicide

SIR: The advice of Neil S. Kaye, M.D., and Stephen M. Soreff, M.D. (1) to "contact the family as soon as possible" and "tell them of all the efforts to treat the patient before the suicide" (p.740) did not adequately warn of potential legal or clinical complications. Confidentiality continues beyond death (2, pp. 163–165). A psychiatrist is liable for harm caused by disclosures about deceased patients. This crucial caveat was omitted from the article by Dr. Kaye and Dr. Soreff.

The proposed family interventions omitted discussion of disturbed families whose members are causes or indirect targets of the suicide. For example, in my own practice or supervision the following have occurred.

1. A patient's family was characterized by pathological boundary disturbances. The relative who found the body demanded secrecy about the cause of death, claiming that the knowledge would lead others to commit suicide and would "destroy" family relationships.

2. A patient had a secret history of sexual abuse by a family member and while alive had expressed to her therapist strong wishes that the family never know about her need for treatment. Another clinician's postsuicide family intervention triggered demands by a suspicious member to reveal what had been alleged in treatment.

3. A patient committed suicide in a symbolic manner after an ordinary social act by a family member was experienced as an abandonment. If the clinician had revealed the nature of the suicide, it seemed likely that the family would have ostracized the member whose ordinary act had "precipitated" the suicide.

Drs. Kaye and Soreff implied that other recommendations can be implemented separately from risk management. Thus, advice to communicate with the hospital staff and other patients to minimize adverse effects omitted evaluation of possible legal contingencies. In speaking to staff and patients, one may transform them into potential witnesses. Thus Simon (2, p. 457) advises consultation with an attorney and/or malpractice carrier before making any oral or written statements about an adverse clinical event.

Dr. Kaye and Dr. Soreff presented the malpractice carrier as an optional rather than an essential player in risk management. Giving no reasons, they stated, "Notifying the malpractice insurance carrier *may be* [emphasis added] part of managing the risk. However, we feel this should not be done without first obtaining legal counsel; often it will depend on the practice setting" (p. 742). This prior legal consultation seems unnecessary. It is unlikely that any attorney would advise a client not to notify the malpractice carrier. Furthermore, some policies may include clauses requiring timely notification about risks. While there are advantages to obtaining additional independent legal counsel, this cannot substitute for communicating with the carrier's attorney.

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SIR: In their otherwise excellent article, written with a great deal of sensitivity, there is conflict between Dr. Kaye's and Dr. Soreff's recommendations concerning doing "grief work" with the family and physicians' ethical considerations. Psychiatrists engage in family therapy on behalf of living patients. When a patient commits suicide, while it is humane and appropriate to meet with the family and to attend the funeral, I do not believe that the psychiatrist should engage in therapeutic exploration of the family's feelings relating to the suicide. Engaging in this kind of therapy fosters the development of new transference relationships. If a family, regardless of whether there is justification, should wish to sue because of the patient's suicide, the fostering of transference between the psychiatrist and the family, even through a single session of grief work, is likely to induce restraint upon the family's decision making. It is not the psychiatrist's responsibility consciously or unconsciously to interfere with the family's decision about whether to litigate.

We have lawyers and physicians providing seminars on prevention of malpractice litigation who deliberately do this very thing: instruct their audience how to influence families emotionally not to sue. As the authors pointed out, a psychiatrist who has rendered quality care should have nothing to fear in instances of frivolous litigation. Unless psychiatric treatment is requested by the family, family therapy following suicide can be construed as unethical behavior.

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## Dr. Kaye and Dr. Soreff Reply

Sir: Since the publication of our article, we have been deluged with letters, including requests from 10 foreign countries and numerous residency training programs for permission to use the article as part of their residency training curriculums. We are indeed honored.

Regarding the comments of Dr. Schacht and Dr. Pearlman, we would note that each has raised some valid concerns. We agree that to reveal the secrets of therapy would be improper. Furthermore, we are not advocating that clinicians violate the terms of their malpractice insurance. However, we are quite conscious that malpractice carriers have their bottom line, not the psychiatrist's best interests, at heart. The recent case involving two psychiatrists both of whom were insured by the same carrier should convince psychiatrists of this (1).

Both of our colleagues seem to have missed the critical point of the article. First, implicit in their arguments is the notion that if a patient commits suicide, something went wrong which is the fault of the psychiatrist. In reality, suicide does happen. It is a fact of diseases and of practice. Second, doctors are human. The response to a patient's death, especially a suicide, requires a human response. Talking with staff, family, and other patients is advised because it is the natural thing to do and not because we are trying to influence potential witnesses. We must be brave enough to move away from the defensive malpractice paranoia and recognize that along with the family, we too share in the loss.

Furthermore, much has been written about dealing with suicide and suicidal patients. Until now, almost all of it has centered on everyone except the psychiatrist. Now is the time to recognize and to accept that when a patient commits suicide, we need to make time for ourselves as well as for everyone else involved.

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## Familial Trichotillomania

Sir: In a letter to the Editor (1), Jacob Kerbeshian, M.D., and Larry Burd, M.S., citing the statement in *DSM-III-R* that familial cases of trichotillomania have not been reported, noted the interesting case of a patient with trichotillomania who had two siblings who also engaged in hair pulling. While little recognized, there have been a number of previous references to familial trichotillomania. For example, Sanderson and Hall-Smith (2) noted a 50-year-old mother with trichotillomania whose 31-year-old daughter also engaged in hair pulling. Similarly, Galski (3) noted two sisters, aged 25 and 27 years, who had pulled out and eaten hair since childhood; since both had begun to pull out hair at about the same time, the author suggested that one might have modeled her behavior after that of the other. Swedo and Rapoport (4) noted that 5% of first-degree relatives of trichotillomanic probands had trichotillomania.

Of 161 adults, adolescents, and children with trichotillomania seen at our clinic, 13 (8%) had first-degree relatives who had pulled out hair (unpublished data). We have now seen two cases of trichotillomania in identical twins; however, neither twin pair was concordant for the behavior. Such observations suggest a possible hereditary predisposition, although Galski's comments regarding modeling should also be given serious consideration.

In 1922 Davis (5) reflected on his 1914 experience with "pseudo-alopecia areata" in an orphanage containing 300 girls under the age of 14; 174 cases of hair loss, characterized by small patches of hair broken off close to the surface, were noted, including three cases in adult staff members. Scalp examinations failed to reveal any clear etiology, and the condition eventually cleared. One year later, another epidemic of 42 cases was noted. Having subsequently seen several cases of hair loss in children secondary to head rubbing and scratching, Davis rejected his earlier theory that the epidemic of alopecia was infectious in nature, noting that cases had developed too rapidly to be explained in this way. Instead, he was of the opinion that these were examples of "mass suggestion" and that the hair loss had resulted from unintentional scratching and rubbing, behavior that was reinforced by attention from attendants and other residents of the orphanage. In a 1933 discussion of trichotillomania (6), Davis referred to the hair loss as the result of hair pulling. Hair pulling in close relatives of trichotillomanic persons, therefore, may not only reflect genetic tendencies toward the disorder but also the impact of environmental modeling. Several hair pullers in our clinic initiated hair pulling after observing another person with the behavior, and families of children with trichotillomania have reported siblings threatening to pull out their hair in order to get their way. The initial concern at presentation for several mothers with trichotillomania was that their children might imitate their behavior.

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## Further Comments on Trichotillomania

SIR: In their article, Gary A. Christenson, M.D., and associates (1) discussed the hypotheses that trichotillomania (hair pulling) is a variant of either depression or obsessive-compulsive disorder, but they did not explore its relation to eating disorders, despite noting a high frequency of this comorbidity. In addition. they did not record whether their subjects gave histories of sexual abuse or disclosed significant unresolved sexual conflicts, despite these having been postulated by other authors (2, 3) as possible etiological factors in trichotillomania.

As well as confirming the finding of others that the large majority of hair pullers are female (3), the authors also found that 20% admitted to a history of bulimia nervosa or an atypical eating disorder. Greenberg and Sarner, in their 1965 study (3), found that 12 of the 16 women in a series of 19 patients with trichotillomania "showed a striking overconcern with their weight which went far beyond the usual American woman's concern with slimness, and which amounted to a true somatic preoccupation," despite their normal weight. Since then, other authors (4–6) have reported bulimia nervosa and trichotillomania as coexisting pathologies, including one report of three cases from a series of five bulimic patients which implied that trichotillomania (and trichophagy) might be a common but usually concealed complication of bulimia (6). There is also some evidence that the antibulimic antidepressant fluoxetine can be effective in treating trichotillomania as well (6).

Given that persons with bulimia can be reluctant to disclose their disordered eating, and that this diagnosis is associated with a high prevalence of wide-ranging secondary affective pathology, many of those presenting with trichotillomania could have a hidden concurrent eating disorder. A common etiological factor might be unresolved sexual conflicts that are suppressed through a repetitive (but not necessarily obsessional) pattern of disordered eating, hair pulling, or both and which might lead either directly, or through the effects of the abnormal behavior, to further psychiatric morbidity.

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SIR: The report by Dr. Christenson and associates on hair pulling is problematic because of the extent to which the authors "pathologized" the habit. They asserted that hair pulling is associated with other psychiatric conditions and did not temper their assertion with exceptions. In fact, the authors used the term "psychiatrically disabled" at least twice to describe hair pullers. However, the pediatric, behavioral, and dermatological literatures on hair pulling describe mostly cases in which hair pulling presents as a benign habit that is easily treated with behavior modification, counseling, or even placebo-type interventions. Dr. Christenson and associates imprudently dismissed these literatures by arguing that hair pulling has not been shown to be similar to other benign habits such as thumb sucking. This argument reflects unfamiliarity with existing literature, important aspects of scientific method, or both. Several studies have shown that hair pulling can covary with thumb sucking (1–4), and the designs used in most of them are among the most conservative in science. The findings show that the two habits are often similar and are sometimes even functionally equivalent.

Quite simply, there appear to be different populations of hair pullers. For example, the behavioral literature routinely describes hair pullers without coexisting psychopathology (3, 4). On the other hand, the psychiatric literature describes mostly cases in which hair pulling is part of a constellation of problems. The disparity in the two literatures may reflect variable referral patterns, different subtypes, or a spectrum of severity.

The point of this letter is that at least some (perhaps many) human beings who engage in hair pulling are otherwise normal. Many papers on hair pulling (not just the one by Dr. Christensen and associates) ignore this well-documented point and argue that psychopathology is a necessary co-condition of hair pulling. I assert that such papers do little to help any hair pullers and may actually do harm to those who are otherwise normal.

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## Dr. Christenson and Associates Reply

SIR: Dr. Tattersall raises some interesting questions concerning the relation between hair pulling and eating disorders and suggests that these two disorders may share a common etiological factor: unresolved sexual conflicts secondary to a history of sexual abuse. Although we have seen several cases in which a past history of sexual abuse appears to be directly related to the onset of the patient's hair pulling, such an association has been unusual in our experience. Of our initial 60 subjects with trichotillomania, 10 female patients and one male patient (18% total) reported histories of sexual abuse. From Dr. Tattersall's comments, one might hypothesize that these individuals would also have had eating disorders, yet only two subjects had histories of hair pulling, eating disorder, and sexual abuse.

It remains unclear how common the comorbidity of eating disorders and trichotillomania is. In our series of 60 trichotillomanic subjects, 20% had current or past eating disorders, suggesting that the two disorders frequently occur together. It is unlikely that we missed additional cases of eating disorders; we found, as did George et al. (1), that patients appear to find it easier to talk about their eating behavior than their hair pulling.

To clarify further the relation between trichotillomania and bulimia nervosa, we systematically assessed 65 subjects with bulimia nervosa and 40 normal control subjects for the presence of trichotillomania, suspecting that we would find a high number of trichotillomanic persons in the bulimia nervosa group (2). Contrary to our predictions, only one subject with bulimia nervosa and one control subject had trichotillomania, suggesting that the overlap of bulimia nervosa and trichotillomania may not be as common as we and others (1) had suspected. Although Dr. Tattersall cites recent reports of the efficacy of the antibulimic antidepressant fluoxetine in supporting an association between trichotillomania and bulmia nervosa, the open nature of these studies and the possible contribution of motivational factors in these patients must be taken into account. A recent placebo-controlled, crossover study of fluoxetine in trichotillomania completed by our group did not support the efficacy of fluoxetine for this disorder (3).

The observations we have reported here do not support sexual abuse as a necessary or common etiological factor in the development of trichotillomania. A high comorbidity between trichotillomania and eating disorders has been only weakly supported by our data, but further data will need to be collected to answer this question definitively.

In response to Dr. Friman, it is not clear how we "pathologized" the habit of chronic hair pulling. We simply described psychiatric comorbidity that had been systematically assessed in a sample of chronic hair pullers who were primarily self-referred. Dr. Friman appears to ignore our finding that some of our subjects had no additional psychiatric pathology and our acknowledgment that our findings of high rates of psychiatric comorbidity may have been an artifact of sampling. We clearly stated that those whose problems are limited to hair pulling may be less likely to seek help.

Dr. Friman states that we argued that "hair pulling has not been shown to be similar to other benign habits such as thumb sucking"; on the contrary, we suggested that hair pulling might serve a function similar to that of nail biting. We never meant to infer that hair pulling automatically implies that psychiatric comorbidity is present; however, we would caution that failure to look for it may be a great disservice to the patient.

We would agree that the disparity between the psychiatric literature and the other literature on hair pulling may reflect variable referral patterns, subtypes, or a spectrum of severity. We clearly identified our sample as adult chronic hair pullers; our subjects may differ greatly from younger patients or those whose hair pulling may be more brief in duration, although our initial experience with children and adolescents who pull out hair suggests that psychiatric comorbidity is not uncommon (4). Differences in the two literatures might additionally reflect theoretical biases of the researchers and methodological incongruences as well. Dr. Friman claims that the "behavioral literature routinely describes hair pullers without coexisting psychopathology" but fails to acknowledge the lack of systematic assessment for other psychopathology in, and the limited extent of, this literature. In their 1984 review of the behavioral literature, Dr. Friman and associates identified only 25 reports on hair pulling (mostly case reports) covering a total of 64 cases (in eight of which the subjects were mildly to profoundly retarded); they referred to the methodology of the largest study, which included 34 of the 64 cases, as "quasi-experimental." The behavioral, pediatric, and dermatological literature has yet to include reports of systematic evaluations for psychiatric comorbidity in large subject populations.

Not all behaviorists view hair pulling as a simple habit. Mansueto (5), who recently evaluated over 40 people with trichotillomania, stated that his data "challenge the widespread impression that trichotillomania is a simple nervous habit. Instead the problem is revealed as a complex disorder with great variation in individual expression."

We feel that discussing the full spectrum of hair pulling, including psychiatric comorbidity, does more service to hair pullers than to isolate hair pulling as the only problem during assessment or treatment of the disorder or to assume its benign or limited nature on the basis of location of presentation or researcher/therapist bias.

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*Reprints of letters to the Editor are not available.*

# APA Council Reports

*At the fall component meetings of the American Psychiatric Association in Washington, D.C., on Sept. 11–15, 1991, the APA councils heard reports from their components. Following are summaries of the activities of the councils and their components.*

## The Council on Addiction Psychiatry

Roger E. Meyer, M.D., Chairperson

The Council on Addiction Psychiatry and its subcomponents have a strong commitment to providing psychiatric leadership in the growing field of research, prevention, and treatment of addictive disorders. The council will continue to provide recommendations to APA on training and treatment issues. Currently, two components report to the council.

The *Committee on Training and Education in Addiction Psychiatry,* Robert Niven, M.D., chairperson, continues to discuss the current status of training, both clinical and research, in addictive disorders. At its meetings this year, the committee discussed various training issues, including added qualifications in addiction psychiatry, the Consortium for Medical Fellowships, and a continuing education training project for psychiatrists in the prevention and early identification of alcohol and other drug abuse problems.

The *Task Force on Psychiatric Services for Addicted Patients,* Steven Mirin, M.D., chairperson, was recently established 1) to evaluate the different types of available treatment and advise the council on important issues affecting the role of psychiatry in the treatment of addictive disorders, 2) to monitor, evaluate, and give advice on issues involving current and new funding mechanisms and problems, including coverage under various funding schemes, and 3) to alert the council and the field, when appropriate, if problems or important issues become obvious. At its first meeting, on Sept. 11, 1991, the task force spent a great deal of time discussing the role of psychiatrists in substance abuse treatment and appropriate funding mechanisms for this treatment. The importance of liaison with other APA components and outside organizations was emphasized during this discussion. The task force also reviewed the "Criteria for Levels of Care for Reimbursement," the "American Society of Addiction Medicine's Patient Placement Criteria for the Treatment of Psychoactive Substance Use Disorders," and the Medicaid Substance Abuse Treatment Act of 1991.

The council itself considered a number of important items during the year. A great deal of time and effort has been spent on the proposal for added qualifications in addiction psychiatry. Late last year APA's Assembly of District Branches voted to approve this proposal. Recently the American Board of Psychiatry and Neurology (ABPN) and the American Board of Medical Specialties approved APA's recommendation for these added qualifications. APA, through the council, will continue to work with the ABPN on the development of a certification examination, to be presented in the next few years.

At its meetings throughout the year, the council spent a great deal of time discussing the possible reorganization of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). The council is concerned not only about the future of research at the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse but also about the role of psychiatrists in the services system and the need for careful evaluation of prevention and treatment demonstration projects. At its meeting on Sept. 12, 1991, the council expressed its concern about the lack of an official APA stand concerning this reorganization. The council agreed to communicate to the APA Work Group on Federal Government Organizational Structure, the Joint Commission on Government Relations, and the Board of Trustees a set of principles to be included in APA's recommendations concerning this reorganization.

The council discussed the possible development of practice guidelines for substance abuse treatment. The council has expressed its desire to work with the Steering Committee on Practice Guidelines in developing such guidelines.

Because it agrees that nicotine dependence is a major public health problem, the council discussed the possible development of a task force on nicotine dependence. This task force, which would report to both the Council on Addiction Psychiatry and the Council on Research, would educate psychiatrists regarding the seriousness of nicotine addiction and the need for treatment; assess current scientific information in the field related to clinically relevant basic science data, treatment approaches, and implications of comorbidity with other psychiatric conditions; recommend reimbursement issues that need to be explored; develop recommendations for training and curriculum development for psychiatric residency programs; and establish a general research agenda. This recommendation was approved by the Joint Reference Committee in October 1991 and is scheduled to be presented to the Board of Trustees for its final approval in December. The council continues its involvement in the ADAMHA Primary Care/Substance Abuse Linkage Initiative, which was established to strengthen the links between and integration of the primary health care system and the alcohol abuse, drug abuse, mental illness, and HIV/AIDS treatment systems. Recently the council forwarded names of individuals for consideration as speakers at the upcoming Secretarial Conference on Primary Care and Substance Abuse Linkage.

The council recommended that APA support the Women and Alcohol Research Equity Act as a bill that would require additional funding. This recommendation was approved by the Board of Trustees and was communicated to Congress by the Division of Government Relations.

The council recommended that APA support the Medicaid Substance Abuse Treatment Act of 1991, recognizing that treatment services should also be covered in appropriate settings other than residential ones, under medical supervision. The council also recommended that APA become an organizational member of the National Coalition on Alcohol and Other Drug Issues. These recommendations were approved by the Joint Reference Committee in October 1991 and are scheduled to be presented to the Board of Trustees in December for its final approval.

The council looks forward to addressing several important issues related to addiction psychiatry in the coming year. These issues include continued development of a certification examination for added qualifications in addiction psychiatry, programs for clean needle and syringe exchange, and the inclusion of detoxification in the American Medical Association's basic insurance benefits package.

# The Council on Aging

Jerome A. Yesavage, M.D., Chairperson

The Council on Aging has had an extremely productive year. Two components completed their reports, and publication by APA is now pending. A third report is expected to be completed and approved for publication in early 1992. The Board of Trustees has approved the establishment of the council's second committee, the Committee on the Ethnic Minority Elderly. The council also received approval to establish the Work Group on Model Standards for Private Long-Term Care Insurance. Finally, the Task Force on the White House Conference on Aging has convened an interdisciplinary coordinating group to assist in the preparation of a mini-conference on mental health in anticipation of the 1993 White House Conference on Aging.

Council members continue their extensive collaboration with other APA components and offices and with other medical organizations. For example, the Council on Aging will participate with the Council on Psychiatry and Law in the work of the intercouncil Subcommittee on the Impaired Driver. The Council on Aging will work closely with the Council on Medical Education and Career Development to monitor issues related to education and training in geriatric psychiatry. The Council on Aging continues to maintain close working relationships with APA's Division of Government Relations and with the National Institute of Mental Health (NIMH).

In 1990 the council initiated a formal working relationship with the American Association for Retired Persons (AARP) and recommended to the Joint Reference Committee and the Board of Trustees that APA also participate in AARP activities. In 1991 council members represented APA at meetings of the AARP mental health forum; other council members worked with an AARP leadership group on health care policy. The council is also closely cooperating in the design and dissemination of an AARP-sponsored survey on nursing home care issues, and individual council members provided guidance to AARP staff in development of AARP publications of interest to the elderly population.

Council members routinely provide expertise and advice on complex federal laws and regulation governing the care of the elderly. In response to the request and guidance of one member of the council, Senator John Chafee (R-R.I.) recently introduced federal legislation to repeal the discriminatory Medicare 50% copayment required of nursing home residents who receive mental health care.

In response to a coordinated effort by the Council on Aging and the APA Division of Government Relations, committees in the U.S. Senate and the U.S. House of Representatives have approved legislation to facilitate federal assistance to programs for education and training in geriatric psychiatry.

Members of the Council on Aging were particularly active in conveying to their federal elected officials their concerns about the impact on geriatric psychiatry of the new resource-based relative value scale (RBRVS) Medicare fee schedule; the final rule on the RBRVS as published in late November substantially improved Medicare payment to psychiatry under the new fee schedule. The members of the Committee on Long-Term Care and Treatment for the Elderly have been particularly effective in assisting the APA Division of Government Relations in commenting on, and obtaining changes in, proposed federal regulations governing the general care and treatment of nursing home residents, in particular, regulations governing the use of psychotropic medications for the nursing home population.

Virtually all council components met during the 1991 annual meeting in New Orleans, and they also met during the 1991 fall component meetings in Washington, D.C. The council will also convene for its January 1992 meeting in Washington, where members will meet with key Congressional staff and with members of Congress. The January meeting provides a unique opportunity for the members of the council to develop personal and professional relationships with Congressional staff and members of Congress who are directly involved in the development of federal policy affecting geriatric psychiatry and in other federal issues of concern to the council.

The *Task Force on the White House Conference on Aging,* Sanford Finkel, M.D., chairperson, reported that, after numerous false starts, the President finally announced the convening of a decennial White House Conference on Aging in 1993. In preparation for the White House conference, the task force is working with representatives of the psychology, social work, and nursing professions to develop an agenda for a mental health mini-conference to be held before the 1993 White House Conference on Aging. With support from NIMH, representatives of the four disciplines met in Washington in October 1991 to review the record of the last White House Conference on Aging (in 1981) and to prepare a paper for NIMH on the progress toward meeting the mental health goals adopted by that conference. This paper, which is preparatory to the mini-conference, is already well underway; a second meeting of the coordinating group will be held in January 1992 to complete work on the paper.

The *Committee on Long-Term Care and Treatment for the Elderly,* Ira Katz, M.D., chairperson, and the *Task Force on Reimbursement Options and Alternatives in the Psychiatric Care of Older Persons,* Howard Goldman, M.D., chairperson, continue to meet concurrently. At the direction of the Council on Aging, the committee jointly sponsored with NIMH a 1-day panel on the use of psychotropic medications for the elderly nursing home population. The panel led the committee to propose a position statement on the use of psychotherapeutic medications for nursing home residents. (The position statement was approved by the Assembly of District Branches in November 1991.) The panel will also lead to the development of a supplement to the committee's 1989 report on the mentally ill elderly in nursing homes (1).

Members of the committee and the task force continued to provide expert assistance to APA's Division of Government Relations on issues related to nursing home care and federal reimbursement for psychiatric services under the Medicare program. To that end, Dr. Goldman was a featured speaker at a Division of Government Relations presentation to key Congressional health care staff on the proposed RBRVS rule and its adverse impact on psychiatry.

In response to a Board directive, the committee and the task force recommended that APA establish a work group on model standards for private long-term care insurance to develop and recommend policy standards aimed at eliminating discrimination in long-term care insurance against individuals requiring treatment for mental illness. Current insurance standards governing the issue are extremely weak. Although the Work Group on Model Standards for Private Long-Term Care Insurance was approved, funding is still pending. The work group hopes to begin its work in 1992.

The *Task Force on Models of Practice in Geriatric Psychiatry,* Marion Goldstein, M.D., chairperson, has completed its draft report. Council consideration of the draft report is expected in early 1992. In addition, the task force conducted a workshop on comparative models of practice at the APA 1991 annual meeting.

The *Task Force on the Ethnic Minority Elderly,* Kenneth M. Sakauye, M.D., chairperson, completed its report, which was subsequently approved for publication by the Joint Reference Committee and the Board of Trustees. One of the recommendations was that the task force be converted to a permanent committee. That recommendation was approved, and the task force became the Committee on the Ethnic Minority Elderly. The committee will meet beginning in 1992, and it will work closely with APA components, such as the Council on National Affairs, on issues of mutual concern.

The *Corresponding Task Force on Geriatric Psychiatry in the Public Mental Health Sector,* Barry Fogel, M.D., chairperson, completed its report, "Geriatric Psychiatry in the State Mental Health System." The report was subsequently approved for publication by the Joint Reference Committee and the Board of Trustees. Publication is expected in the near future.

The *Task Force on Education and Training in Geriatric Psychiatry,* Charles Shamoian, M.D., chairperson, has seen the fruition of its major federal legislative initiative: the expansion of federal support to programs of education and training for geriatric psychiatry. To that end, committees in the U.S. House of Representatives and Senate have approved legislation to amend Title VII of the Public Health Service Act to expand opportunities for fellowship funding for training in geriatric psychiatry and to permit departments of psychiatry to be a locus of geriatric training. Final federal legislative action is expected in early 1992.

In conclusion, the Council on Aging and its components expect 1992 to be another busy and productive year, marking anew the impact the council continues to have on key health care policy issues affecting the care and treatment of geriatric patients.

## REFERENCE

1. American Psychiatric Association: Nursing Homes and the Mentally Ill Elderly: Task Force Report 28. Washington, DC, APA, 1989

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# The Council on Children, Adolescents, and Their Families

Mohammad Shafii, M.D., Chairperson

The council continued to address its charge—to maximize APA's effectiveness in addressing the mental health needs of children, adolescents, and their families—in every aspect of its work.

At the close of the May 1991 meeting, Dr. Shafii assumed leadership of the council from Dr. Lawrence Stone, who was appointed to serve as a consultant. Dr. Donald Gair was appointed as a new member of the council. Drs. Clarice Kestenbaum and James MacIntyre, who had been appointed as corresponding members, were available to participate in person at the May meeting. Dr. Richard Athey, APA/Burroughs Wellcome Fellow, and Dr. Alice Mao, APA/NIMH Fellow, rotated off the council. In September 1991 the fellowship positions were filled by Drs. Michael Kaplan and Cydney Parker.

The *Committee on Chronically Ill and Emotionally Handicapped Children,* Cynthia Pfeffer, M.D., chairperson, established an active liaison with the Committee on the Chronically Mentally Ill, which is housed within the Council on Psychiatric Services. In addition, the committee has met with representatives of lay groups. Both of these efforts have helped the committee in its deliberations about community services for chronically mentally ill children and adolescents. To provide a smooth transition, Dr. Pfeffer assumed the role of consultant when Dr. Kendon Smith was appointed chairperson of the component. The council accepted Dr. Smith's recommendation that APA request the National Institute of Mental Health (NIMH) and private foundations to solicit proposals for epidemiological studies of chronic mental disorders in children and adolescents.

The *Committee on Family Violence and Sexual Abuse,* Sandra Kaplan, M.D., chairperson, developed a position statement on child abuse (1), which was approved by the council and subsequently by the Joint Reference Committee and the Board of Trustees. A major effort of the committee has been the development of "Family Violence: A Clinical Guide." It is anticipated that the book will be completed in the near future.

The *Committee on Psychiatry and Mental Health in the Schools,* Irving Berkovitz, M.D., chairperson, completed the "Position Statement on School-Based Health Clinics" (2), which was approved by the council, Joint Reference Committee, and Board of Trustees. The committee is close to completing a monograph, "Psychiatric Involvement in the Schools." The committee intends to develop a shorter version of the document for distribution to school districts and to assess the interest of district branch presidents and editors of district branch newsletters in forming networks of psychiatrists who consult in schools.

The *Work Group to Develop a Handbook for Psychiatric Practice Related to the Juvenile Justice System,* Michael Kalogerakis, M.D., chairperson, completed the *Handbook of Psychiatric Practice in the Juvenile Court.* The book is being published by the American Psychiatric Press and will be available by the end of 1991. Expressing thanks for an excellent job, the council voted to disband the component and to express appreciation to the Kenworthy-Swift Foundation for funding the project.

Even though deeply saddened by the sudden and unexpected death of member Dr. Edward Futterman, the *Committee on Juvenile Justice Issues* continued to operate smoothly as the leadership shifted from Dr. William Buzogany to Dr. Richard Marohn. The committee completed a report, "The Psychiatrist and the Juvenile Justice System" (3), and is in the process of reworking the "Position Statement on the Capital Punishment of Minors." After a review of the available data related to the charge of inappropriate hospitalization of adolescents, the committee recommended the establishment of a task force on the use and abuse of hospitalization of children.

The *Task Force to Study the Use and Abuse of Hospitalization,* Elizabeth Weller, M.D., chairperson, held its first meeting in September 1991. The component plans to be a clearinghouse for the accumulation and storage of information and guidelines developed by other organizations, to review data bases, to develop a position paper on practice guidelines for physicians, and to develop facts for families.

Pursuant to the recommendation of the Board of Trustees, which provided money for the first meeting of the component, staff is seeking outside funding for the continuation and completion of the assignment of the task force.

The *Task Force on the Psychiatric Aspects of New Reproductive Technologies,* Miriam Rosenthal, M.D., chairperson, expects to complete its monograph by winter 1992. All recommendations will pertain to psychiatry, although the task force is multidisciplinary.

The *Task Force on Day Care for Pre-School Children,* Myron Belfer, M.D., chairperson, developed a position statement on day care. The group emphasized the importance of day care, that sometimes it is not a matter of choice for parents but a necessity. The APA membership is being asked to maintain constant vigilance about day care, as is the Joint Commission on Government Relations. Groups of residents and fellows within APA are also being asked to lobby for ongoing attention to day care.

Each component developed a workshop or symposium for the 1991 annual meeting. The council joined Board of Trustees member Herbert Sacks, M.D., in planning and participating in an annual meeting workshop on custody and visitation.

The council has developed active liaisons with the Council on International Affairs (regarding the plight of Rumanian children and children in the Near East), the Council on Research (regarding ongoing NIMH funding for research on children and adolescents), the Task Force on the Homeless Mentally Ill (under the Council on Psychiatric Services), the Committee on Human Rights (under the Council on International Affairs), and the Committee on the Chronically Mentally Ill (under the Council on Psychiatric Services).

The council received a report on the development of the Board of Adolescent Psychiatry and plans to develop a formal response. After a review of materials that address the development of a subspecialty in neurodevelopmental pediatrics, the council recommended that APA communicate to the American Academy of Pediatrics and the American Board of Pediatrics APA's concern about the lack of coordination in the development of curricula for specialists who serve children and youth. The council has also recommended development of dialogue regarding coordinated planning to best meet the needs of children and youth.

## REFERENCES

1. Position statement on child abuse and neglect by adults (official actions). Am J Psychiatry 1991; 148:1626
2. Position statement on school-based health clinics (official actions). Am J Psychiatry 1991; 148:820
3. The psychiatrist and the juvenile justice system (official actions). Am J Psychiatry 1990; 147:1584

# The Council on Economic Affairs

Robert Gibson, M.D., Chairperson

The activities of this council and its components during 1991 reflect APA's continued efforts to influence the many commercial and governmental entities that affect the provision of psychiatric care. Members of the council and its components maintained liaison with representatives of such organizations as the Social Security Administration, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the Health Care Financing Administration (HCFA), and major managed care and insurance companies.

The *Committee on Financing and Marketing,* Robert O. Friedel, M.D., chairperson, has focused on marketing assistance for APA members, primarily through the district branches. Its major concerns include negative trends in corporate response, decreasing insurance benefits for psychiatric care, inappropriate utilization management activities, and a blurring of the roles of psychiatrists and psychologists. The committee has set the following goals for the year: 1) updating the APA marketing manual for district branches, 2) reviewing and editing a new chapter on marketing psychotherapy for inclusion in the manual, and 3) submitting a workshop proposal for the 1992 annual meeting.

The *Committee on Hospital-Based or Hospital-Related Services,* Boris Astrachan, M.D., chairperson, involved itself with an analysis of the efforts of the JCAHO to improve communication with participating organizations and restructure the professional and technical advisory committees. The committee alerted the council that the restructuring could significantly weaken the professional and technical advisory committees and diminish the role of participating organizations. The committee will continue to take a proactive stance and urge the JCAHO to strengthen the professional and technical advisory committees and improve their functioning. The committee also reviewed and commented on research conducted through a National Institute of Mental Health (NIMH) grant relating to a model mental health benefit.

The *Committee on Interprofessional Affairs,* William Webb, Jr., M.D., chairperson, continues its work with the Joint Commission on Interprofessional Affairs. The commission is made up of representatives from APA, the American Psychological Association, the National Association of Social Workers, and the American Nurses' Association. In 1991 the joint commission engaged in efforts to define each of the professions represented by the four organizations. It is anticipated that the document, "Content of the Professions," will be published in 1992. Additionally, the Joint Commission on Interprofessional Affairs continued its planning for a 1993 conference on interdisciplinary collaboration and explored many issues of mutual interest, including managed care, national health insurance, prescribing privileges for psychologists, and continuing education.

The *Committee on Managed Care,* Steven Sharfstein, M.D., chairperson, continues to address issues for psychiatry and managed care through support of legislation and regulation, research, education, and dialogue with the managed care industry. Special projects this year included publication and distribution to the membership of "Utilization Management: A Handbook for Psychiatrists," sponsorship with the Ethics Committee of the Conference on Ethics in Managed Care for Psychiatry (publication and distribution of the conference proceedings is anticipated), an annual meeting workshop on ethics in managed care, activation of the network of district branch managed care liaisons and initiation of local efforts in managed care, and initiation of a series of meetings with managed care organizations to discuss problems documented through APA's 800-number telephone service and to seek redress at the policy level. The committee continues to support managed care regulation activities, the continuing review and presentation of cases documented through the 800-number (1-800-343-4671) telephone service, and support of medical necessity criteria review in conjunction with other APA components.

The *Committee on Occupational Psychiatry,* Peter L. Brill, M.D., chairperson, has had a very full agenda during 1991, has submitted proposals for two workshops and a component workshop for the 1992 annual meeting, and is preparing a course for the 1993 annual meeting. During the year three text books, one of which will be published by American Psychiatric Press, Inc. (APPI), were written by psychiatrists who are members of the committee. The committee further reported that the Academy of Occupational and Organizational Psychiatry will meet in January 1992 and at the APA annual meeting in May. The agenda of the January meeting includes managed care, cultural change, and organizational consulting.

The *Committee on Quality Assurance,* George F. Wilson, M.D., chairperson, has completed its revision of the *Manual of Psychiatric Quality Assurance* with the assistance of other components and with peer review by multiple members of the association. The revised manual is now scheduled for publication by APPI in December of 1991. It is hoped that it will be useful for reviewing the history of the Association's involvement in utilization review activities and that the publication of the criteria used by the utilization reviewers will be helpful to members currently engaged in managed care. The Committee on Quality Assurance has been reconstituted as a smaller committee. During the last year it has begun its review and critique of the various criteria, standards, and screens affecting psychiatrists that are published by other organizations and the federal government. A great deal of time has been required for the review of the HCFA generic quality screens for hospital inpatient care, which have come under some criticism by members because of the use of the screens in general hospital psychiatric units, where they do not seem to be appropriately applied. It is hoped that the very precise and in-depth review and commentary given by the committee will be useful as the Association seeks to carry on its negotiations with the HCFA to work out meaningful revisions in the generic quality screens for hospital inpatient care. This is an example of the work the Committee on Quality Assurance will continue to do as it carries out its new charge.

In its initial meetings, the newly formed *Committee on Universal Access to Health Care,* Herbert S. Sacks, M.D., chairperson, refined its mission and planned its agenda. The committee's tasks are 1) to disseminate information to the broad membership relating to universal access to health care, through articles in APA publications and through programs at the annual meeting and regional meetings, 2) to develop a knowledge base and keep abreast of developments in health care economics as they pertain to universal access to care, 3) to study global issues involving health care delivery systems, 4) to serve as a resource to the Board of Trustees as it develops APA policy on universal access, and 5) to interact with other APA components both to receive relevant input and to provide consultation as indicated. The committee's specific activities will include preparation of a bibliography identifying approximately six publications on universal access and submission of a number of articles to *Psychiatric News* on topics such as developments in the states, international developments, and Congressional actions.

The *Task Force on Prospective Payment Issues,* Joseph T. English, M.D., chairperson, continued to monitor payment issues and to explore potential alternative payment mechanisms. Among these efforts was a review of NIMH studies of federal legislative and administrative activities related to prospective payment for psychiatry. The task force believes there are no immediate threats to psychiatry's exempt status, and it continues to work closely with the Prospective Payment Assessment Commission as it works to improve reimbursement under the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA). The task force is monitoring several innovative payment reform initiatives underway in the states. These are being watched closely by the federal government and the field.

The *Work Group on Codes and Reimbursement,* Chester Schmidt, Jr., M.D., chairperson, conducted an in-depth review of the *Physicians' Current Procedural Terminology, 4th edition* (*CPT-IV*), which will be published by the American Medical Association. The APA membership will be educated about the evaluation and management codes through presentation of a workshop at the November 1991 meeting of the Assembly and an article to be published in *Psychiatric News.* Additionally, proposals for a course on *CPT* basics and a workshop for the 1992 annual meeting have been submitted. The work group reported that it will resurvey the Medicare intermediaries to determine whether there are problems in giving psychiatrists access to the evaluation and management codes.

The *Work Group on the Harvard Resource-Based Relative Value Scale Study,* Donald Scherl, M.D., chairperson, continues to address the proposed RBRVS Medicare fee schedule. Although the RBRVS was expected to result in an increase in payments for "cognitive" services, including psychiatry, the HCFA proposal would in fact be highly damaging to psychiatry, cutting average payments for psychiatric services by 9% in 1992 and by 5% over the full 5-year phase-in. The HCFA proposed the percentage cut primarily because it included a $3 billion "behavioral offset" fund in its budget. The HCFA anticipated this fund would be needed to offset an increased volume and intensity of services by physicians when payments are reduced under the new fee schedule. Through a complex budget procedure, the behavioral offset would be "leveraged" onto undercompensated cognitive services, resulting in a 16% payment cut.

Numerous statistical, methodological, and conceptual flaws in the proposed RBRVS for psychiatry have been identified. They include problems with data collection and analysis, undervaluation of the relative values for psychiatric work, cross-specialty links, geographic factors, and more. Concluding that the RBRVS proposed for psychiatry is so fundamentally flawed that it could not be fixed by the October 1991 publication of the final rule, APA sought a 1-year delay in its application to psychiatry.

APA and the work group testified before the several relevant committees of the U.S. House of Representatives and Senate, submitted initial comments on the proposed rule, communicated APA concerns to all 535 members of Congress, and coordinated a massive APA grassroots letter-writing campaign. Additionally, APA concerns were communicated during meetings with senior HCFA policy staff. During a 1-day meeting, experts in health economics analyzed the proposal and assisted in the preparation of APA's response. Some 45 pages of final comments were submitted, as well as additional HCFA-requested materials relating to specific RBRVS "fixes" to address psychiatry's concerns. Further, APA hosted a briefing on the RBRVS for the members of the Republican Health Task Force in the House of Representatives.

# The Council on Internal Organization

Charles B. Wilkinson, M.D., Chairperson

The council oversees "all those matters involved in the organizational structure of the Association not covered by constitutional committees." Eleven components report directly to the council, and 15 other components report to committees under the council: 11 award boards report to the Committee on Grants and Awards, and three subcommittees and a task force report to the Scientific Program Committee. Components of the council cover many areas of responsibility: 1) annual meetings—including program content, exhibits, arrangements, and awards given during meetings in recognition of outstanding achievement, 2) information systems—including data processing and telecommunications, 3) benefits offered to members and to APA staff, 4) maintenance of the APA headquarters building, 5) advertising policy, and 6) the federation of auxiliary organizations. Following are the highlights of council and component activities over the past year.

The *Committee on Advertisers and Exhibitors,* Maurice J. Martin, M.D., chairperson, recommended in September 1991 that the revised guidelines on pharmaceutical or other industry-sponsored symposia be expanded to include the Institute on Hospital and Community Psychiatry, as well as the annual meeting. The committee continues to monitor exhibitors' activities during meetings to ensure compliance with the established guidelines. These guidelines, approved for the annual meeting by the Board of Trustees in 1983, were expanded this year to include the H&CP institute.

The *Committee on Advertising,* William D. Strathmann, M.D., chairperson, serves as an advisory body to the editors of APA's three periodicals (*Psychiatric News, American Journal of Psychiatry,* and *Hospital & Community Psychiatry*) on questionable advertisements that either have been submitted for publication or are being considered for solicitation for publication. The committee works closely with the Committee on Advertisers and Exhibitors to keep the latter informed about advertisements it recommends for rejection. As of October, the committee had not been asked by the editors to review any advertisements in 1991. The committee reviewed only two advertisements, both for screening tests, in 1990.

The primary goal of the *Committee on Friends of the APA,* Linda Logsdon, M.D., chairperson, is to identify, recruit, and organize spouses and partners of APA members who are not eligible for the APA Auxiliary or the Lifers Group. The one group under the committee at this time is the APA Auxiliary, which includes spouses of APA members.

The *Committee on Grants and Awards,* Mary Jane England, M.D., chairperson, is reorganizing the Association's awards program, as requested by the Board of Trustees in March 1990. The Board was concerned about the adequacy of the oversight provided by councils to the awards components. The goal of the reorganization is administration of each award by a council that deals with the particular area of the award; i.e., an award for child psychiatry would be administered by the Council on Children, Adolescents, and Their Families. Discussions with the councils concerning assignment of specific awards are continuing. While the reorganization is being further developed, the Board requested an interim measure: presentation to the Board in September 1991 of a list of award winners who will give lectures during the 1992 annual meeting. Other committee actions include the following: 1) the recommendation that the "Foundations' Fund Prize" be changed to the "APA Award for Research," 2) finalization of criteria for the Human Rights Award, which is given to individuals or organizations exemplifying the capacity of human beings to protect others from harm inflicted by other human beings, and 3) approval of the William Sorum Awards, a group of Assembly awards for district branches with significant achievements in Member-in-Training involvement.

The *Headquarters Committee,* Lucy D. Ozarin, M.D., chairperson, continues to oversee the routine functions of the headquarters facility and to review specific issues when they arise. The council directed the committee to review its charge with emphasis on carrying out its designated functions.

The *Committee on History and Library,* Martha J. Kirkpatrick, M.D., chairperson, is seeking outside funding for the Rare Books Room within the APA Library and hopes that the room will be completed in time for APA's Sesquicentennial celebration in 1994. The committee is planning activities in conjunction with the Sesquicentennial, including workshops, preparation of a bibliography of rare books, and a photography exhibit.

The *Committee on Human Resources,* Jack W. Bonner III, M.D., chairperson, was formerly the Personnel Committee. This committee recommended a number of additions to the APA personnel manual, including policies on conflicts of interest, ethics, drugs in the workplace, sexual harassment, and smoking. The committee has asked staff to explore ways of reducing benefit costs and the feasibility of offering flexible benefits to staff.

The *Committee on Information Systems,* Zebulon C. Taintor, M.D., chairperson, has found that APA's course in data processing is highly cost-effective and is progressing well and reasonably. The challenge of data processing in a setting such as APA is to orchestrate the acquisition of hardware and software so that the individual components can carry out their myriad, diverse functions while preserving a core of common software and backup support. The committee is also considering how best to work with the Steering Committee on Practice Guidelines on software for the guidelines. As a service to members, the committee held a workshop during the 1991 annual meeting and plans to hold another in 1992.

Allan Tasman, M.D., chairperson of the *Scientific Program Committee,* reported that the 1991 annual meeting in New Orleans had over 13,000 attendees and was among the top three annual meetings ever in terms of attendance. The committee continues to refine the program, adding formats such as the newly established Round Table Discussions and Forums, both of which will become a regular part of the program. Continued funding of sign-language interpreters during APA's annual meetings is being discussed with the Caucus of Hearing-Impaired Psychiatrists and Psychiatrists Working With Hearing-Impaired Patients.

Two changes in the exhibits have been suggested: 1) suspension of solicitation and display of scientific exhibits at annual meetings and H&CP institutes, beginning with the 1992 annual meeting, since these exhibits seem to have been absorbed by the scientific program, and 2) an increase in the fees for industry-sponsored symposia, beginning with 1993 annual meeting.

The *Committee on Special Benefit Programs,* Eva V. Ebin, M.D., chairperson, continues to develop member programs, including the Legal Consultation Plan and Gold MasterCard. The Member Retirement Planning Program, in effect for 8 months, has received a great response: more than 2,000 members have requested and received prospectuses and questionnaires. The "Law and the Practice of Psychiatry" and "Career Choices in Psychiatry" seminars continue to thrive. Other programs being developed include discount office equipment (such as fax machines).

The *Committee on Telemedical Services,* Jonathan D. Lieff, M.D., chairperson, is unique in medicine, since it monitors developments in telemedicine, a field that has great potential both for helping the suffering and for exploitative and hazardous misuse. The council recommended that the committee focus on the committee's original charge: defining the ethical use of telecommunications in medical services, clarifying medical-legal problems, reviewing potential activities with other medical groups, and studying the cost-effectiveness of teleconferences versus in-person meetings. The council is also discussing with the committee its functioning, the value of telecommunications for psychiatry, and the future work of the committee.

Also discussed by the council was a proposal, presented by APA management staff, for saving money on APA travel by contracting with a vendor to provide the lowest applicable nonrefundable air fares. This proposal was subsequently presented to the Board by the Budget Committee and approved.

The council would like to thank Dr. Thelissa Harris for stepping in as acting chairperson during the fall component meetings, when neither the chairperson nor vice-chairperson was available.

# The Council on International Affairs

Eugene Feigelson, M.D., Chairperson

The Council on International Affairs is the membership component that oversees APA's international activities and makes policy recommendations to the APA Board of Trustees related to activities international in scope. It deals with all questions pertaining to psychiatry and international relations that are presented by APA members, other components, psychiatrists from other countries, and staff.

The council and the components that report to the council have initiated a number of important projects this year, and the council has taken on the responsibility of defining APA's role in the "new world order." The council is involved in projects that can potentially affect many countries in the world and projects that are more regional. In addition, the Office of International Affairs has close contacts with psychiatrists in over 80 countries around the world, and these contacts have proven to be valuable resources for APA members, especially in the area of patient referrals and collaborative ventures.

This year one of the projects that has been a focus of the council's work is our bilateral exchange with colleagues in Poland, Czechoslovakia, and Hungary. This exchange will take place from March 25 to April 12, 1992, in Krakow, Poland; Prague and Bratislava, Czechoslovakia; and Budapest, Hungary. Funding is being provided by the Upjohn Company. A team of 12 American psychiatric experts are traveling to these countries to present lectures on areas of mutual interest and to receive information about these special aspects of psychiatry in each country. If funding is secured for this project in future years, the next phase will focus on Romania, Bulgaria, and the Baltic states and in subsequent years it will involve other parts of the world.

The council was pleased with the very successful joint meeting with the Caribbean Psychiatric Association, which was held in Barbados in May 1991. More than 200 APA members attended this meeting, which focused on substance abuse, forensic psychiatry, mental health delivery systems, children, and geriatrics. Special appreciation is extended to Dr. Richard Fields of Atlanta and to Dr. George Mahy of Barbados for their leadership in making this conference such a success. This was the last in a long series of jointly organized scientific conferences sponsored by APA and psychiatric organizations in other countries. The council was compelled to suggest that these meetings be ceased unless additional staff is allocated for the Office of International Affairs, and APA's diminishing financial resources preclude the addition of staff. The Office of International Affairs does maintain an extensive international meetings list, which can be distributed on request.

APA has agreed with a council recommendation that APA cosponsor a Soviet-American conference on ethics in psychiatry with the Georgetown-Johns Hopkins Universities Program in Law, Ethics, and Health; the University of Wisconsin Program in Medical Ethics; and the Yale Law School Schell Center for International Human Rights. Dr. Loren Roth has been appointed as the official APA representative to serve on the organizing committee for this conference, and the process for nomination of Soviet members has begun. This conference will probably take place in late 1992 or early 1993.

The council continues to be pleased with the International Scholars Program at the APA annual meeting and would like to express its appreciation to the Scientific Program Committee for its efforts in increasing the number of international presentations on the annual meeting program. It is hoped that the services and assistance available for international visitors will be enhanced at the 1992 annual meeting. Approximately 2,000 participants from other countries attend each annual meeting, and the council would like to make them feel as welcome as possible.

The *Committee on International Education,* Normund Wong, M.D., chairperson, is disappointed that the International Medical Scholars Program administered by the Educational Commission on Foreign Medical Graduates no longer includes psychiatry because of the lack of funding. APA's Committee on International Education was to provide the psychiatric component of that project. However, the committee and the council are hoping to obtain outside funding for establishment of international guidelines for psychiatric curricula. The first phase of the project would bring together distinguished psychiatric educators from South and Central America for a series of seminars to discuss these issues and make proposals that could be shared with educators in the United States and other countries. If the first phase is successful, funding would be sought to continue these seminars in other parts of the world. Collaboration with the InterAmerican Council of Psychiatric Organizations and the Pan American Health Organization will be sought as the project moves ahead.

In addition, this committee and the council are seeking outside funds for an international directory of psychiatry that would build on the network already established by the Office of International Affairs. Key psychiatric officials around the world would be surveyed with specific questions of interest. Once the information was obtained, the directory would be published and available for distribution. The specific areas to be covered relate to psychiatric training, certification, services, demographic characteristics of mental health professionals, and major mental health concerns in each country.

The *Committee on Human Rights,* Loren Roth, M.D., chairperson, has now completed the booklet "Psychiatry and Human Rights" and has submitted it for consideration by the APA leadership. This booklet discusses reasons for psychiatric involvement in human rights issues and provides information about APA's work in this area. The committee is especially pleased with the new APA Human Rights Award, which will be presented for the first time at the APA 1992 annual meeting. Nominations have been received from the APA membership, and efforts to obtain outside funding for the award are still underway. The committee has also received approval for an official APA form for inquiries into individual cases of alleged human rights abuses. The committee has written a number of letters of inquiry about individual cases and hopes that an official APA inquiry form will increase the likelihood of response.

The committee and APA President Lawrence Hartmann are organizing a Presidential Symposium on "Psychiatry and Human Rights," which will be presented at the 1992 APA annual meeting. Presentations will made by Dr. Chester Pierce, Mr. Eric Stover, Dr. Inge Kemp Genefke, Dr. Samuel Martinez-Lara, and others.

The *Committee on International Abuse and Misuse of Psychiatry and Psychiatrists,* D. Raymond Freebury, M.D., chairperson, has continued to monitor psychiatric abuses around the world and to make recommendations to the APA leadership for possible action. The committee was very interested in the World Psychiatric Association's site visit report on Soviet psychiatry, which was written by a team headed by Dr. J.L.T. Birley of Great Britain. APA members on this team included Dr. Loren Roth, Dr. Vladimir Levit, Dr. Felix Kleyman, and Dr. Ala Levit. However, the report revealed that the All Union Society of Psychiatrists and Narcologists of the Soviet Union has been, at best, only perfunctory in its efforts to meet some of the conditions outlined by both the World Psychiatric Association (WPA) and APA. Thus, the Board of Trustees indicated that in the light of political developments in the Soviet Union, the WPA should be prepared to expand its contacts with Soviet psychiatry by recognizing recently established and newly emerging psychiatric associations as they fulfill the standards and requirements of the WPA. In addition, the Board of Trustees believes that the All Union Society's membership in the WPA should be revoked. The committee continues to seek additional ways to help psychiatric associations that wish to eliminate political abuse of psychiatry in their countries.

The council has asked the committee to begin work on an international "bill of rights" for patients, which might be submitted to the WPA for its adoption. A number of countries around the world have not adopted mental health laws that would protect patients' rights, and in others patients are not informed of their rights. The use of psychiatry for political purposes is not uncommon in many parts of the world, although it is rarely used to the extent as in the Soviet Union in past years. The committee is actively seeking ways to facilitate the work of the newly emerging independent psychiatric organizations in preventing the recurrence of these practices in the future.

The committee has written to over 150 pharmaceutical companies to obtain copies of their international guidelines for drug trials and testing in other countries. There have been allegations in the past that the standards in effect in the United States are not always used in other countries, and the committee is looking into these allegations.

The committee has organized a symposium for the APA annual meeting: "Psychiatric Abuse, Abusers, and Scientific Exchanges." The symposium will include presentations on Romanian psychiatry, the politics of Soviet psychiatry, an analysis of the Soviet psychiatric literature, and issues related to scientific exchanges with individuals involved in psychiatric abuse.

The *Task Force on Conflict Resolution,* R. Curtis Bristol, M.D., chairperson, has organized an innovative workshop for the APA annual meeting, and the council is pleased and honored to have Ambassador Max Kampelman present "Conflict Resolution and the World of Diplomacy," in which he will discuss his experience as head of the U.S. delegation in bilateral negotiations on nuclear and space arms in Geneva.

The task force is also seeking outside funding for a 3-year collaborative study designed to produce a theory defining and explaining the process of conflict resolution. To further theoretical development in the field of conflict resolution, the task force plans to establish a scholars' working group of social scientists, which initially will assess and synthesize current theoretical contributions and then develop a theory to expand on the process of conflict resolution. This task force intends to publish a document produced by the collaborative effort of its scholars working group, which is meant to pave the way for further debate and for testing of the theory in practical application, both internationally and nationally.

The *Task Force on the Psychosocial Aspects of the Middle East Peace Process,* George Tarjan, M.D., chairperson, will probably be reactivated in light of the current developments in the Middle East and numerous requests by colleagues and others in that part of the world for APA's assistance in bringing individuals together as it has done in the past. The council has asked for additional appointments to the task force so that these requests can be examined, and a proposal to the APA leadership might be forthcoming. After a specific proposal is approved by the APA Board of Trustees, outside funding would be required before any substantive project could be undertaken.

The council has discussed issues related to the WPA and is trying to find ways to help strengthen that organization in a way that would benefit all of its members, including APA. Many organizations around the world look to APA for assistance in areas that might otherwise be handled by the WPA, and if APA is to remain a member of the WPA, it should do everything possible to ensure the viability of the WPA's work. The council has recommended that the Task Force on Liaison with the WPA, Eugene Feigelson, M.D., chairperson, be disbanded and has taken over the charge to that task force.

In addition, the council is planning ways to further its collaboration with international allied organizations, and in the future it will invite representatives of different international organizations to make presentations about their work at the September meeting of the council. There is much that we can learn from each other, and the council believes collaboration of this sort will be very valuable.

The council appreciates the assistance APA members have provided to colleagues in the newly emerging democracies of the world through the APA Office of International Affairs. It is looking for ways to involve the APA membership at large in international collaboration, and members are encouraged to contact the office with any suggestions about how this goal might be furthered.

# The Council on Medical Education and Career Development

Jerald Kay, M.D., Chairperson

The council has overall responsibility for all issues and efforts related to medical education, both for psychiatrists and, where appropriate, other physicians. Its responsibility includes promoting quality education and training for medical students and residents, as well as continuing education activities for practitioners. It is involved with activities related to subspecialties and special areas of clinical interest, such as child and adolescent psychiatry, consultation-liaison psychiatry, and administrative psychiatry. In collaboration with its 17 components, other APA components, and related psychiatric organizations, the council has been very active in the recruitment of medical students into psychiatry.

In addition, the council also has primary responsibility for implementing and monitoring the APA continuing medical education (CME) requirement of the membership in order to promote the highest quality of psychiatric care and to encourage continued professional growth of psychiatrists.

The council convened a meeting of representatives of the American Board of Psychiatry and Neurology, Inc. (ABPN), the Residency Review Committee for Psychiatry (RRC), and the APA Committee on Graduate Education and Commission on Subspecialization to address issues related to subspecialty fellowship training programs. The group focused its discussion on the need for accreditation of all subspecialty fellowship programs and for certification of persons completing such programs. To continue the dialogue, the group will meet again in September 1992 during the APA component meetings.

The *Committee on Administrative Psychiatry,* Stephen Rachlin, M.D., chairperson, reported the results of the oral portion of the certification examination in administrative psychiatry, held on May 11, 1991, during the annual meeting in New Orleans. Of the eight candidates examined, two passed and have been certified, four "conditioned," and two failed. Dr. W. Walter Menninger was named the recipient of the 1992 Administrative Psychiatry Award.

The *Committee on Consultation-Liaison Psychiatry and Primary Care Education,* Fawzy I. Fawzy, M.D., chairperson, proposed establishment of a subcommittee on psychiatric aspects of life-sustaining technology to define the contribution psychiatry can make to the understanding of patient, family, and caregiver attitudes and behavior toward the critically and terminally ill. Further, the subcommittee will identify the proper role of psychiatry and psychiatrists, in particular, in dealing with the clinical and ethical issues in the care of such patients.

The committee has submitted an application for added qualifications in consultation-liaison psychiatry and primary care education, which is being reviewed by the APA Commission on Subspecialization. The committee continues to strengthen its liaisons with the Society of General Internal Medicine and the American Academy of Family Practice, and it is collaborating with Dr. Robert Hales on a proposed project to develop the *DSM-IV* version for primary care.

The *Committee on Graduate Education,* James H. Shore, M.D., chairperson, reported on its newly defined liaison with the APA Commission on Subspecialization and its collaborative work to evaluate new subspecialty proposals and the potential impact on educational issues for postgraduate training resources in psychiatry. It has sought an expanded dialogue with the ABPN and the RRC concerning the process and outcome of accreditation of new subspecialties and certification of individuals completing them. The status of geriatric, addiction, and forensic psychiatry was carefully reviewed. The committee supports the strongest possible emphasis on research training for each new subspecialty.

Residents' concern about the risk of HIV infection through needle stick was addressed by the committee. The Accreditation Council for Graduate Medical Education is developing guidelines for disability insurance. The committee will disseminate these guidelines and review the issue with the Committee of Residents and Fellows.

The recruitment of medical students into psychiatry was fully addressed, and presentations were given by the presidents of the American Association of Directors of Psychiatry Residency Training and the Association of Directors of Medical Student Education in Psychiatry. The committee will work jointly with the Council on Medical Education and Career Development to stimulate a national dialogue and to pursue identified initiatives for recruitment.

The *Committee on Continuing Education,* Pauline Langsley, M.D., chairperson, reported on the new Accreditation Council for Continuing Medical Education "Essentials" for accreditation as a cosponsoring organization for CME programs. The Essentials require that APA, to continue as an accredited cosponsor, be actively involved in needs assessment, faculty selection, and evaluation for all APA-cosponsored CME programs.

The committee proposes that APA, through coordination in the Office of Education, solicit and designate annual meeting courses which provide an overview of psychiatry and assist members in acquiring board certification.

The *Committee on the Impaired Physician,* Malkah T. Notman, M.D., chairperson, has developed "Guidelines for Mental Health Services for Medical Students and Residents." If this document is approved, it will be submitted for publication to *Academic Medicine.* Production of an educational videotape on physicians' impairment, which will use interviews of physicians and patients, is underway.

A subcommittee of the committee has been formed to develop operational definitions of impaired judgment, incompetence, and negligent behavior of physicians. This subcommittee will report back to the committee in May 1992. It is also working with the Commission on AIDS and the Committee on Gay, Lesbian, and Bisexual Issues on HIV infection in physicians, with an emphasis on the biopsychosocial dimensions of impairment.

The *Committee on Medical Student Education,* Carol A. Bernstein, M.D., chairperson, continues to address issues affecting graduate medical education and the substantial decrease in the recruitment of medical students into psychiatry. The committee discussed the need for coordinated and sustained initiatives in this area and specifically focused on the necessity of obtaining support from departmental chairpersons. In this regard, the committee felt that each department of psychiatry should be encouraged to identify a director of medical student education who is at least half-time. It plans to conduct an informal telephone survey of medical schools that have been most effective and least effective in recruiting students into psychiatry over the past 5 years, to help clarify salient recruitment variables.

Specific recruitment activities include coordination of the distribution of the APA Division of Public Affairs' film series to every medical school in the country. The films will provide guidance to local resident groups and encourage them to discuss career possibilities in psychiatry with medical students. In addition, the committee will be promoting the development of medical school senior-year electives within psychiatry residency programs, in collaboration with the Association of Directors of Medical Student Education in Psychiatry and the American Association of Directors of Psychiatry Residency Training. The committee will continue to send representatives to the annual conventions of the American Medical Student Association and the Student National Medical Association, which remain excellent opportunities to meet and speak with students regarding careers in psychiatry.

The first issue of *Lucid Associations,* a medical student newsletter, was distributed to all Medical Student Members of the Association. Committee members will also be writing a series of articles for the *New Physician* (published by the American Medical Student Association), for the *Psychiatric Residents' Newsletter* (published by the Committee of Residents and Fellows), and for *Psychiatric News* to highlight issues relevant to medical students and medical student education.

In May 1991 the recipients of the first Nancy C.A. Roeske, M.D., Certificate for Excellence in Medical Student Education were honored at the third annual Medical Student Day luncheon. There were 48 recipients of the certificate; 11 were voluntary faculty and 37 were salaried, and they represented medical schools from every region of the country. The committee reviewed 61 applications for the 1992 certificate, and those selected will receive their certificates at the annual meeting in May 1992.

Medical Student Day and the annual luncheon for medical students, residents, and training directors continue to be enormous successes at the annual meeting. Over 250 people attended the 1991 luncheon, including medical students, residents, Roeske certificate recipients, and distinguished APA leaders. If outside funding can be obtained, the fourth annual Medical Student Day luncheon will be held in 1992.

To increase its effectiveness, the committee plans to work closely with other organizations, such as the Association of Directors of Medical Student Education in Psychiatry, the American Association of Directors of Psychiatry Residency Training, and the Association for Academic Psychiatry, which are also dedicated to recruitment and education of medical students.

The *Committee of Residents and Fellows,* Mary Marshall Overstreet, J.D., M.D., chairperson, continues to address the educational aspects of a wide range of issues affecting psychiatry and psychiatric education and training. These issues include student loan indebtedness, prescribing privileges for psychologists, access to health care, and the resource-based relative value scale (RBRVS) reimbursement plan. The committee is working with the Division of Government Relations and the other APA resident groups to assist residents in planning individual discussions on these political issues with their respective Congressional representatives during the APA annual meeting in May 1992.

The committee is especially concerned about the lack of both formal ethics instruction in general and role modeling for specific situations, such as interacting with third-party payers. Additionally, the potential adverse impact on psychiatric education that could emerge from the trend toward subspecialization within the field is being discussed with other concerned components.

Recruitment of medical students into psychiatry also continues to be of great concern. The committee discussed ways in which residents can become more active in recruitment efforts, such as improving liaison with medical colleagues, providing role models and education to medical students early in their training, and continuing to demystify and demythicize the work of psychiatry.

The committee continues to write and publish the *Psychiatric Residents' Newsletter* and serves on the editorial board of the *Jefferson Journal of Psychiatry.*

The *Steering Committee, Psychiatric Knowledge and Skills Self-Assessment Program VI (PKSAP VI),* Gordon Strauss, M.D., chairperson, reported that all three modules (A, B, and C) are available as a package. Each module provides 48 hours of category I CME credits, and there are no deadlines for submission of answer sheets for central scoring. Program participants will receive confidential scoring (through assignment of an individual code), a CME certificate, a critique, and a reference book.

The *Task Force on Educational Activities for Diagnostic Systems,* Michael Fauman, M.D., chairperson, completed the initial diagnostic practice survey and analysis of the implementation of *DSM-III-R* by psychiatrists. The survey was sent to a random sample of 931 APA members, and there was a 64% response rate (N=596). On the basis of the data collected, the task force concluded that a follow-up survey is needed to explore the different subpopulations of responders to the first survey and to help design additional educational materials.

The task force feels that its name is cumbersome and does not accurately reflect the specificity of its functions. It has recommended that its name be changed to the Task Force on Diagnostic Education.

The task force continues its collaborative work with the Task Force on DSM-IV and the Committee on Diagnosis and Assessment.

The *Task Force to Facilitate Communication Between APA and ABPN,* Rodrigo Munoz, M.D., chairperson, has focused on increasing the number of minority directors on the ABPN Board of Directors and the number of minority physicians who serve as examiners. It has also renewed its efforts to obtain ABPN assistance in creating APA-sponsored courses for physicians who are applying for certification. The task force feels that the process will be expedited if examiners are permitted to participate in APA courses.

The *Task Force on Post Residency Fellowship Programs,* George Pollock, M.D., Ph.D., chairperson, completed its work and prepared an appendix of fellowship programs, which accompanies the *Directory of Psychiatry Residency Training Programs* (1). Further, the task force recommended that APA convene a meeting of representatives from APA, the ABPN, and the RRC to discuss accreditation of subspecialty fellowship programs and certification of individuals who complete such training.

The *Task Force on Recertification,* Joe Tupin, M.D., chairperson, completed its charge "to study existing and proposed recertification activities of other medical specialty organizations" and has developed recommendations for recertification programs in psychiatry. The Board of Trustees accepted the task force's final report and its recommendation that the task force be disbanded and a permanent standing APA component be established to work with ABPN representatives on developing educational programs to help members prepare for recertification and initial certification.

The *Committee of Young Psychiatrists,* Mary Ellen Foti, M.D., chairperson, continues to be concerned about retention of APA members as they advance from Member-in-Training to General Member status. It is working with the Committee on Membership to develop studies that may provide data on the extent of the problem and its causes. Additionally, the committee has developed a model survey of young psychiatrists that will provide data on practice patterns, professional concerns, and other issues of concern to "young psychiatrist" members of the Association (those who are younger than 40 years or have practiced less than 5 years).

The committee believes that the primary concerns of young psychiatrists relate to early career development, and this issue will be the focus of a workshop and breakfast session at the annual meeting in May 1992.

Through the efforts of Drs. Paul Putman (Delegate) and James C.V. Chou (Alternate Delegate), the committee remains active in the Young Physicians Section of the American Medical Association.

The *Work Group on Recertification,* Gordon Strauss, M.D., chairperson, convened for the first time in September 1991. The work group focused its discussion on the ABPN's tentative plans for establishing recertification and the need for APA to make recommendations that will appropriately affect the ABPN's final plan.

The *Subcommittee on Certification,* Gerald Melchiode, M.D., chairperson, convened for the first time in September 1991. The subcommittee discussed various ways APA could help its members prepare for certification and plans to develop information on useful sources of assistance.

The *APA/Mead Johnson Fellowship Selection Committee,* Stuart Keill, M.D., chairperson, selected the 1991–1992 APA/Mead Johnson Fellows during its June 1991 meeting, and there were no major discrepancies in the ranking among the members of the committee. Forty-two nominations were received, from which 15 fellows were selected. It was agreed that the selection process would remain substantially as is.

The committee reviewed the process for inviting nominations and agreed to make certain refinements to the solicitation process.

The *Selection/Advisory Committee of the APA/NIMH Minority Fellowship Program,* Charles Pinderhughes, M.D., chairperson, selected seven of the 18 residents who applied for the 1990–1991 fellowship program. In addition, the committee selected four alternates and named five 1989–1990 fellows as trainee consultants.

The committee sought approval to publish, as a monograph, the proceedings of the 1986 symposium "Ethnic Difference: Do You Amend Your Therapeutic Approach?"

The *APA/Burroughs Wellcome Fellowship Selection and Program Committee,* Roger Peele, M.D., chairperson, reviewed 50 nominations for the 1991–1993 program and selected 10 new fellows.

On behalf of the Burroughs Wellcome Company, Mr. Jerald Breitman presented a check for $115,000 for financial support of the fellowship at the May 1991 meeting of the Board of Trustees. A reception was hosted by the Burroughs Wellcome Company for current and former APA/Burroughs Wellcome (formerly Falk) Fellows, representatives of the Maurice Falk Medical Fund, and APA members and staff who have been involved in the program.

The research symposium held during the September component meetings featured the presentations "Developing a Risk Profile in Vietnamese Amerasians" (Alice Mao Brams, M.D., Chief Resident, Division of Child Psychiatry, Cullen Bayou Place, Baylor College of Medicine) and "Psychiatric Research Opportunities at NIMH" (Samuel Keith, M.D., Acting Deputy Director of NIMH and Acting Director of the Division of Applied Services Research). In addition, a current APA/Burroughs Wellcome Fellow (James Hudziak, M.D., Washington University School of Medicine) presented "A Survey of Obstacles to Doing Research as a Psychiatric Resident."

The fellows discussed the need for continued participation of APA/Burroughs Wellcome Fellows in APA, both at the national and local levels, so that they can retain and practice the skills acquired during the fellowship. The program continues to be a highly valued channel for the training of tomorrow's leaders in psychiatry.

## REFERENCES

1. APA Office of Education Staff: Directory of Psychiatry Residency Training Programs, 5th ed. Washington, DC, American Psychiatric Association, 1991

# The Council on National Affairs

### Fred Gottlieb, M.D., Chairperson

This council is responsible for matters of national interest to psychiatry and the patients it serves. Social and health-related issues that adversely affect underrepresented and underserved groups in the general population and within the profession elicit particular attention by the council. The council works closely with representatives from the Assembly and other APA components and with APA staff. The 11 components that specifically report to the council include those representing the six designated minority groups, the Committee on International Medical Graduates, and four components dealing with other relevant national issues: psychiatry's abuse and misuse, nuclear issues, disasters, and the relationship of psychiatry and religion.

Dr. James Thompson chaired the May meeting, during which the council approved a resolution thanking Dr. Lindbergh Sata, whose council tenure was ending, for his leadership and wise counsel.

In September the council initiated reconsideration of its past, present, and potential contributions to the profession, our patients, and the organization. The council has been an important locus, in which advocacy for the temporarily unempowered has been marshalled and in which innovative solutions have been sought and valued. Council members stressed that in addition to responding to issues referred to it, the council should initiate activities, reaching out to and nurturing its components with ideas, as well as advice and encouragement. The council plans to meet in February to continue reevaluating its structure, functions, and goals. It is aware of the risk of being considered parochial, when in fact its interests are flexible and far-ranging, in keeping with its charge. The council's liaison to the Board of Trustees suggested that a multicultural curriculum for use in residency training programs may be more integrative than several discrete culturally oriented curricula. Apparently Dr. Leah Dickstein is attempting to devise such a multicultural curriculum, based on proposals from various components of the Council on National Affairs.

When it met with the Joint Commission on Government Affairs, the council requested ongoing updating on legislation about uniform licensure. The council also urged that APA use all Congressional hearings (e.g., Supreme Court nominations) as opportunities to present relevant APA policies, and the council noted that national health insurance is an issue of particular salience for minority and underserved populations, as well as for *all* Americans interested in national affairs.

During the fall component meetings, a representative of the Steering Committee on Practice Guidelines spoke to the council about the development of practice guidelines and asked the council if it was interested in having a formal liaison to the steering committee. The council emphasized the importance of heterogeneous input and representation, among both the reviewers and the work groups, from the many sectors of psychiatry.

A member of APA's Resource Development Committee spoke to the council about a proposed nonprofit foundation that would seek to link the major U.S. minority medical societies, the U.S. Department of Health and Human Services, and the Merck Foundation to address the continuing problems in service delivery, especially to many minority patients. The Urban Health Alliance plans to fund worthwhile minority projects—e.g., in physician recruitment and professional education, clinical studies, illness screening, and patient and family education—and to be involved in appropriate public policy activities.

Following are reports on the activities of the components under the Council on National Affairs.

The *Committee on Abuse and Misuse of Psychiatry in the U.S.,* Ledro R. Justice, M.D., chairperson, discussed the Joint Reference Committee's recommendations on the draft of "Misuse and Abuse of Psychiatry in the U.S.: A Definition and Discussion," particularly the definition of abuse. The committee will review other comments received from members who attended the fall meetings and will then revise the paper. While the focus of the draft was to stimulate discussion of abuse within the psychiatric community, APA has yet to formulate a position statement. The committee is preparing a position statement on abuse and misuse of psychiatry, beyond the current draft.

The committee discussed its mission and agreed that it also should handle individual cases within the guidelines of the committee's charge. It will continue to review cases sent to APA, collect additional information as needed, and report findings to the Medical Director and APA counsel. The council asked that the committee obtain follow-up on the results of prior referrals. The committee also agreed that it would continue to stimulate discussion about abuse and misuse of psychiatry, focus on prevention, and investigate organized systems in which abuse and misuse can occur.

The committee met with Dr. Jeremy Lazarus, chairperson of the Ethics Committee. Examples of individual ethics violations and institutional abuse were discussed in order to compare and contrast definitions and concepts. The consensus was that the work of the two committees overlaps on occasion. It was stressed that the Ethics Committee considers only individual matters and that it has the ability to perform on-site assessments and obtain legal counsel. Dr. Lazarus suggested that a newsletter would be useful in educating psychiatrists and nonclinicians and in eliciting feedback on concerns about abuse and misuse. Dr. Lazarus offered the use of the Ethics Committee's newsletter.

The committee also met with the Committee on Gay, Lesbian, and Bisexual Issues to discuss some of the latter's concerns. Apparently some psychiatrists attempt to change the sexual orientation of patients by means of "reparative therapy," which is based on the invalid assertion that homosexuality is a mental illness. There was some discussion of clinical and treatment issues, including the importance of clinical neutrality and absence of stigma and prejudice on the therapist's part. (See also the discussion of this issue in the report of the Committee on Gay, Lesbian, and Bisexual Issues.)

To determine the usefulness of contacting patient advocacy groups, the committee met with Mr. John Blamphin of the APA Division of Public Affairs. Mr. Blamphin explained how complaints are generally sent to and distributed within APA. Most complaints received by his office would not be referred to this committee. He suggested that the committee not encourage advocacy groups to send complaints but saw no problem in the committee's informing these groups that the committee exists. He also suggested that the committee write to Ms. Laurie Flynn of the National Alliance for the Mentally Ill.

When the committee discussed the decrease in the number of American medical students entering psychiatry, it concluded that such a decrease in the number of psychiatrists poses a risk for abuse of psychiatry because it could lead to further limitations in the adequate treatment of patients who can best afford treatment and less adequate treatment of those less able to pay.

The *Committee of American Indian, Alaska Native, and Native Hawaiian Psychiatrists,* Albert Samuelson, M.D., chairperson, was formerly the Committee of American Indian/Alaskan Native Psychiatrists. Native Hawaiian psychiatrists sought to be part of this committee, and the committee welcomed this addition. The committee asked that Native Hawaiian psychiatrists be represented on the committee and that the committee's name be changed. "Alaskan Native" was changed to "Alaska Native" because "Alaskan" could refer to anyone born in Alaska, whereas "Alaska Native" refers to the ethnic group native to the state. For the same reason, "Native American" could be taken to mean anyone born in America, whereas "American Indian" refers to the ethnic group. By contrast, the Hawaiian psychiatrists chose "Native Hawaiian."

The American Medical Association (AMA), through Project USA, presently offers physicians the opportunity to work for brief periods on reservations in underserved areas. Travel, malpractice insurance, and small stipends are provided. Project USA has not yet offered psychiatrists a similar opportunity to serve. The committee recommends that APA explore with the AMA and the Indian Health Service the feasibility of offering APA members a similar opportunity to serve in public psychiatry through Project USA and other programs. The council suggested that the committee discuss this with the AMA Section Council on Psychiatry and the APA delegate to the AMA.

The committee continues to be concerned about the severe problem of alcohol dependency among Indian people, which has catastrophic health and social consequences. The report of the U.S. General Accounting Office on addiction services on reservations reinforces the pressing need to strengthen these programs. The committee recommended that the Council on Addiction Psychiatry establish liaison with the Indian Health Service and offer APA resources and expertise for resolution of this critical health problem. The council also recommended that the committee discuss this matter with the Council on Addiction Psychiatry.

The *Committee of Asian-American Psychiatrists,* Francis Lu, M.D., chairperson, is involved in a number of projects: recruitment of Asian-American psychiatrists for membership in APA, implementation of the annual Asian/Asian-American Award, facilitation of communication with allied Asian-American psychiatric groups and the Pacific Rim College of Psychiatrists, and outreach to Asian-American psychiatrists and residents at the annual meeting through the component workshop, reception, and breakfast meeting with residents. Given the rapid increase in the Asian-American population, the committee believes its charge remains important to APA and the mental health of Asian-Americans.

The newest charge to the committee, approved in 1990 by the Board of Trustees, is to focus on ways to increase Asian-American membership in APA. This charge is important for APA not only because it could increase the number of members but also because it could increase Asian-American psychiatrists' participation in APA activities. The committee developed three recruitment strategies: recruitment with help from allied organizations, recruitment of Asian-American psychiatric residents, and recruitment of Asian-American medical students interested in psychiatry. All three strategies would involve collaboration with the Committee on Membership and the Office of Membership. The committee's detailed recruitment strategies were presented to the Joint Reference Committee as potential models for replication in other parts of APA.

The committee will present the Asian/Asian-American Award for the first time at the May 1992 annual meeting. The 1992 awards will be presented to Drs. Tsung-Yi Lin and Lindbergh S. Sata. Kun-Po Soo, M.D., Ph.D., of Taiwan, donated $50,000 to endow this award. The committee developed a brochure publicizing the Asian/Asian-American Award along the lines of the one for the Solomon Carter Fuller Award. The council approved the publication of this brochure, subject to approval by the Joint Reference Committee and the Board of Trustees.

The committee prepared a proposal for a new V code, "psychoreligious or psychospiritual problem," which it sent to the Committee on Religion and Psychiatry for its review.

On May 6, 1989, APA and the Pacific Rim College of Psychiatrists cosponsored the First International Symposium on Psychiatric Research, which was organized by the Committee of Asian-American Psychiatrists. The committee has now finished editing the proceedings of that symposium and, with the council's approval, will send it to the APA Editorial Review Panel for its consideration, with a view to publication by APA.

The *Committee of Black Psychiatrists,* Robert T.M. Phillips, M.D., chairperson, revised the language of its charge to better reflect its work. After some small modifications, the revised charge was accepted and submitted to the Board of Trustees.

In previous meetings the committee had discussed drafting a position statement on racial/ethnic harassment. Committee members think that more background work is needed. Committee member Dr. Sheree Dixon and Ms. Alison Bondurant of the APA Office of Minority/National Affairs agreed to research APA's efforts regarding this issue. If the committee finds that APA has taken an adequate position against racial harassment, it will not pursue the matter.

Like other components of the council, this committee wants to become more involved in APA efforts to recruit members. To expedite the process, Dr. Phillips met with the Committee on Medical Student Education, and committee member Dr. Joshua Calhoun met with the Committee of Residents and Fellows and the Committee of Young Psychiatrists. All three committees were receptive to the idea of collaboration with the Committee of Black Psychiatrists.

In response to material from APA's Division of Government Relations, Dr. Phillips encouraged committee members to write to their state legislators and appropriate staff of the U.S. Department of Defense to express opposition to legislation that would give prescribing privileges to psychologists in the military.

The committee selected Dr. Gloria Johnson Powell for the 1992 Solomon Carter Fuller Award.

The *Committee on Gay, Lesbian, and Bisexual Issues,* Richard A. Isay, M.D., chairperson, would like to have better links with national and international groups concerned with gay and lesbian rights and health issues. For instance, the International Lesbian and Gay Association helps members achieve rights worldwide by focusing public and government attention on lesbian and gay rights, by supporting programs, and by exerting diplomatic pressure. It also represents lesbian and gay rights in the work of international bodies, such as the United Nations, and is campaigning for Amnesty International to consider lesbians and gay men imprisoned because of their sexuality as prisoners of conscience. The committee decided not to ask for authorization to apply for membership in the International Lesbian and Gay Association; instead, many committee members who are members of the Association of Gay and Lesbian Psychiatrists will urge that organization to join the International Lesbian and Gay Association.

In September 1990 the committee proposed a position statement on the right to privacy. At the council's suggestion, the committee asked other APA components to review the statement, which it then revised. The council presented the statement to the Joint Reference Committee in June 1991. The Joint Reference Committee referred the proposed position statement on the right to privacy back to the Council on National Affairs and to this committee, with suggestions for further revisions. The committee discussed the Joint Reference Committee's suggestions and revised the position statement, which was approved by the council and then by the Joint Reference Committee in October 1991: "Be it resolved that the American Psychiatric Association supports the right to privacy in matters such as birth control, reproductive choice, and adult consensual sexual relations conducted in private, and supports legislative, judicial, and regulatory efforts to protect and guarantee this right."

The committee discussed how to deal with books that contain explicitly antihomosexual attitudes. The committee cited the new book by Joseph Nicolosi, *Reparative Therapy of Male Homosexuality.* Dr. Isay has talked with Dr. Marshall Forstein (Association of Gay and Lesbian Psychiatrists), Michael Siever (American Psychological Association), and Gary Lloyd (National Association of Social Workers) about organizing some action. Dr. Forstein discussed this further at the annual meeting of the Association of Gay and Lesbian Psychiatrists.

The committee spoke with Dr. Abram Hostetter of the Committee on Special Benefit Programs regarding insurance for domestic partners.

The committee suggested a task force, possibly under the Council on Children, Adolescents, and Their Families, to deal with the problem of suicide among gay and lesbian youth.

The *Committee of Hispanic Psychiatrists,* Eduardo R. Val, M.D., chairperson, reviewed the text and sketches for the comic book *Hablemos,* first published in English under the title *Let's Talk About It.* Copies were made available at the minority/national affairs exhibit booth at the annual meeting in May. In December 1990 the Board of Trustees authorized this committee to seek outside funds for a data base on Hispanic mental health and social services. This data base would include information on psychiatrists, special psychiatric societies, and national organizations. At the committee's fall meeting, Dr. Juan Ramos from the National Institute of Mental Health (NIMH) informed the committee that the current NIMH administration approved $25,000 for this project, which will be housed in the APA Office of Research. Dr. Ramos indicated that funds for the second phase of the project would be available in 1993.

The committee discussed the criteria and procedures for the Simon Bolivar Award in response to a letter from a committee member. After a lengthy discussion, the committee agreed that 1) the committee will consider suggestions from any APA member and 2) a committee member can suggest and endorse a candidate by giving specific reasons and submitting the candidate's curriculum vitae to the committee chairperson. Last May the committee selected Dr. Raquel Cohen for the 1992 Simon Bolivar Award.

Another issue the committee found worrisome is the decrease in the number of medical students selecting the specialty of psychiatry. Besides financial considerations, the committee felt that one reason for this decrease is that departments of psychiatry give less direct faculty time to medical students because of the pressure to increase departmental revenue through activities other than teaching.

The *Committee on International Medical Graduates,* Richard Balon, M.D., chairperson, was pleased that the proceedings of the first three international medical graduate (IMG) regional meetings have been made available to interested parties. These meetings were convened to help IMGs bridge language and cultural gaps, understand the theories underlying the American psychiatric service systems and social issues germane to mental health care, and establish a network for IMGs' emotional and professional support. Because of the favorable reception of these proceedings, the committee sought authorization to seek funds to publish the proceedings of the last two IMG meetings.

Some IMGs who are APA members feel that APA either does nothing for them or is not doing enough. The committee would like these and other members, as well as IMG psychiatrists who are not APA members, to know what APA has done and is doing to help them. To disseminate this information, the committee decided to resume publication of its newsletter, for which the committee received authorization to seek outside funds.

International medical graduates constitute 24% of the APA membership but are very significantly underrepresented within the APA component structure. This committee feels that IMGs on APA committees could present IMG problems pertinent to the committees' work better than could non-IMGs. At the council's request, Dr. Balon checked the current "Directory of Components and Staff" to see how many IMGs are on APA components. The dramatic disparity revealed by this count was presented to the Joint Reference Committee in October.

In the interests of attracting young IMG psychiatrists to APA, promoting cohesiveness within IMG groups, and recruiting and retaining members, the committee would like to hold a work-related reception for IMG residents in psychiatry and leaders of various ethnic groups during the 1992 annual meeting. To do this, the committee asked for authorization to seek outside funds.

The *Committee on Psychological Aspects of Nuclear Issues,* Stephen Shanfield, M.D., chairperson, received permission for non-APA publication of the papers presented at its 1990 symposium. The majority of the presenters were not APA members, and other papers not presented at the symposium will be added to the manuscript. The committee's bibliography on nuclear psychology was published in *PSR Quarterly: A Journal of Medicine.*

Part of the charge to this committee is to identify, evaluate, and synthesize emerging knowledge as the basis for educational approaches both within and outside the medical, behavioral, and social sciences and to disseminate information to the APA membership, selected strategic groups, and the general public. The committee was understandably distressed when its proposal for a symposium on nuclear issues for the 1991 annual meeting was initially rejected. This committee is concerned that its submission for the 1992 annual meeting might meet the same fate because nuclear issues do not fall under any designated rubric of the annual meeting program. The council suggested that the committee emphasize the appropriateness of this submission to the presidential theme.

The committee will also propose a symposium for the 1993 annual meeting. Presenters will include non-APA members, whose expenses the committee would like to defray. For this reason, the committee requested authorization to seek outside funds to pay for the transportation, lodging, and meals of five guest speakers. The council noted that the committee was setting an impressive example by planning a 1993 symposium now.

This committee and a representative from the Council on International Affairs are writing a curriculum on the psychology of international relationships; psychiatry residency training directors are the target audience. The committee would like to have this curriculum published promptly after it is completed, possibly as a curriculum or a bibliography that might be considered educational material suitable for submission directly to the Editorial Review Panel.

The *Committee on Religion and Psychiatry,* Richard Thurrell, M.D., chairperson, is concerned about the lack of representation of non-Judeo/Christian religious traditions and hopes that someone from these other faiths will be appointed to the committee in some capacity. Also, as a result of committee membership rotation, there is no one on the committee from a Jewish background. The committee hopes that this, too, will be rectified when appointments are made.

District branch activities in the area of religion and psychiatry remain a concern to the committee. District branches vary in their interest in and attention to this area of their patients' lives. The committee hopes to find ways to sharpen the district branches' concern about patients' spiritual lives and district branch relations with psychiatrically minded clergy.

The committee continues to be interested in cults of various sorts, particularly as they affect psychiatrically vulnerable persons. Dr. Ruth Barnhouse reports on satanic cults as developments warrant. Because the religious aspects of the "religion" of Scientology remain obscure to many committee members, members of the Association of Mental Health Clergy have promised, through informal liaisons, a report on Scientology as a religion.

Interested in its own history, the committee requested a report from long-time member Dr. William Grosch regarding the origin, initial efforts, and development of the committee.

The committee is still contemplating a brief, loose-leaf book containing numerous in-depth references for all psychiatrists in the vein of "What Every Psychiatrist Should Know About His or Her Patients' Religions." Such a compact volume would presumably inform and sensitize colleagues to the important role that religious belief, conflict, and aspiration might play in the life of a patient of a particular religious heritage.

The committee selected Dr. Paolos Mar Gregorios, Metropolitan of Delhi, for the 1992 Oskar Pfister Award.

The *Committee on Women,* Gail E. Robinson, M.D., chairperson, proposed a position statement on the care of female addicts who are pregnant or have just given birth, after consulting with other APA components. The Assembly and the Board of Trustees approved the statement, which recommended that APA take a leadership role in advocacy for these mothers and their children with departments of social services or their agencies legally responsible for the safety of these children.

In September the committee proposed reaffirmation of APA's position statement on abortion and recruitment and promotion of women and ethnic minorities in psychiatry. Council members questioned the need to reaffirm APA's position, and Dr. Robinson replied that there are efforts by some APA members to erode or even rescind this position statement. The council suggested that the committee use and expand the current statement, taking into account the attempts to erode it, and recommend APA action. In addition, the council suggested that the committee confer with other pertinent components.

After some revisions and consultation with other components, the committee presented its proposal for APA actions regarding reproductive rights, and the council voted to present it to the Board of Trustees as an urgent action item. The Board of Trustees approved this position statement and will forward it to the Assembly for its approval.

National statistics show that after more active recruitment of women into medicine, women now constitute 40% of medical school students. Many of these women specialize in psychiatry, particularly child psychiatry. Despite their numbers, very few are in senior academic positions. It is important to have women and ethnic minorities in senior academic and leadership positions so they can serve as role models, encourage younger women and ethnic minorities, and enhance the areas of study related to women's health, minority health, and parenting. Consequently, the committee recommended that the APA Board of Trustees take a leadership role in advocating recruitment of women and ethnic minorities for senior academic and administrative careers and the promotion of qualified women and ethnic minorities to leadership positions in these areas.

The committee will receive funding from Mead Johnson for an activity center at the 1992 annual meeting. The committee will schedule the following meetings at the center: 1) "What Is Involved in Becoming an APA Fellow (How to Keep Young Psychiatrists Involved in the APA)," 2) "Passing the Board Examinations," and 3) "How to Publish Papers."

So that the committee can remain up-to-date on issues important to women, each committee member will be responsible for a specific topic. The topics include abortion, parental leave, maternal/fetal rights and new reproductive technologies, patient-therapist sexual misconduct, violence against women, and sexual harassment.

The committee reviewed a memo from Dr. Jerald Kay, chairperson of the Council on Medical Education and Career Development, concerning the decrease in the number of American medical students entering psychiatry. The committee noted that this may particularly affect women: staffing may selectively hit areas involving women's mental health, women are more likely to practice in public psychiatry, and there is a disproportionate number of women in child psychiatry. The committee will write to Dr. Kay and will attach a list of suggestions about recruitment.

Dr. Viola Young Horbach, president of the Federation of Organizations of Professional Women, spoke to the committee about pending legal actions concerning the emotional repercussions for women of problems in the workplace. It was suggested that female physicians are in a relatively good position to fight back against discrimination in the workplace because they have the opportunity to go into private practice even if their academic careers are threatened because they speak out. It was also suggested that psychiatry help define the "reasonable woman" standard, which is the court's means of assessing what is reasonably perceived as sexual discrimination. It was suggested that it is important to increase the sensitivity toward these issues in regard to both patients and colleagues, that is, to speak out in communities about such discrimination, to develop policies regarding sexual harassment in the workplace, and to send letters to Dr. Louis Sullivan, Secretary of the U.S. Department of Health and Human Services, and Dr. Frederick Goodwin, Administrator of the Alcohol, Drug Abuse, and Mental Health Administration, asking them to comment on their policies regarding women.

The *Corresponding Task Force on Psychiatric Dimensions of Disasters,* Robert Pynoos, M.D., chairperson, has outlined actions recommended by the APA President in regard to the U.S. National Committee for the Decade of Natural Disaster Reduction. The task force has also asked each district branch to identify a liaison to the task force within the branch. Task force members have successfully collaborated with the American Academy of Child and Adolescent Psychiatry Work Group on Consumer Issues to compile relevant material regarding children and disasters. The task force's next step is to form a network of APA members to be part of a network for disaster response at the local, state, and national levels.

# The Council on Psychiatric Services

James T. Barter, M.D., Chairperson

The Council on Psychiatric Services is committed to furthering the delivery of high-quality psychiatric services. Psychiatrists, whether working in the private sector or the public sector, must constantly wrestle with an overburden of rules and regulations from governmental agencies, third-party payers, and managed care organizations. It is difficult to continue to promote easy access to quality care and services in such circumstances. The reports of the council and its component committees reflect psychiatry's commitment to our patients, our society, and ourselves.

The council has been especially concerned with the psychiatric practitioner, regardless of practice setting. The problems facing psychiatrists are similar and similarly difficult, whether they are working in the public or the private sector. The creation of the Consortium of Chairpersons of APA Components on Public Psychiatry last year was a direct consequence of the realization of the need to be more proactive in dealing with public psychiatry issues. A similar effort focusing on the psychiatric practitioner in private sector settings has begun. It is exquisitely obvious that the solo private practice psychiatrist is beleaguered, bothered, and bedeviled by equally troubling concerns. The council has intensified its interest in dealing with these issues and offers a forum for the views of the private practitioner to be explored, attended to, and disseminated throughout the governing structure of APA. The council has encouraged and recommended the appointment of more private practitioners to APA components to enhance their ability to be heard and involved in policy formation. Structural changes have been suggested, including creation of additional components and reorganization of existing components. These ideas are being actively debated and considered. Last year was challenging and productive, as reflected in the following reports of the component committees and task forces. Next year should be no less.

The *Consortium of Chairpersons of APA Components on Public Psychiatry,* J. Frank James, M.D., chairperson, was established by the Board of Trustees in December 1990 and charged with identifying deficiencies in the delivery of care to groups with special needs and with documenting existing or hypothetical models that address such deficiencies in a cost-effective and clinically sound manner. Accordingly, the group is to prepare information for the APA leadership that may be used for advocacy and other purposes to benefit the psychiatric care delivery system. The consortium reports to and is accountable to the Council on Psychiatric Services.

The consortium includes the chairpersons of the following components: Committee on State and Community Psychiatry Systems, Task Force on the Homeless Mentally Ill, Corresponding Task Force on Geriatric Psychiatry in the Public Mental Health Sector, Committee on Chronically Ill and Emotionally Handicapped Children, Committee on the Chronically Mentally Ill, Committee on Psychiatric Disability and Rehabilitation, the State-University Collaboration Project, Assembly Committee on Community Psychiatry, and Assembly Committee on Public Psychiatry. Others will be invited to participate with the consortium.

The consortium has stressed the need for access to treatment and care for the severely mentally ill and the need to ensure such access in any national health care plan that may emerge. The consortium has also called attention to the need to involve more psychiatrists in the public sector and, hence, the need for incentives for psychiatrists to seek positions or volunteer services in the public sector and recognition of their efforts. Over the past year the consortium has generated many recommendations, which are now in various states of study, approval, and implementation. Recommendations that have been approved by the Board include the following.

1. Advocacy of access to and reimbursement for care for the severely mentally ill that is equal to that for other psychiatric and medical patients.
2. Promotion of psychiatric diagnosis and treatment as an essential component of any rehabilitation program for severely mentally ill persons.
3. Encouragement of public mental health programs to develop ways in which psychiatrists may volunteer or provide services, teaching, supervision, or advocacy.
4. Encouragement of psychiatrists to work in or volunteer some time in public psychiatric programs.
5. Addition of work experience or contribution of time in a public psychiatric program as a category to be considered in decisions on eligibility for APA Fellowship.
6. Inclusion in the next biographical survey, or sample survey, of items intended to clarify amounts of time psychiatrists work or volunteer in public mental health programs.
7. Encouragement of the district branches to develop mechanisms for recognizing those who provide or volunteer direct services to the severely mentally ill.
8. Exploration with pharmaceutical companies of the possibility of supporting programs for recognizing psychiatrists in the public sector, such as a fellowship in an academic center, a traveling or visiting scholar award, or a research sabbatical.

The following are under study by other components.

1. APA promotion of standards for residency training that include a significant training experience in a public health program to prepare residents for career opportunities in public psychiatry (Council on Medical Education).
2. APA encouragement of public mental health programs to develop a forgiveness or "buy-out" program for trainee indebtedness in exchange for a period of service in a public mental health program (Committee on Residents and Fellows).
3. Focus on public psychiatry issues by the biennial State Legislative Institute and Public Affairs Institute (Joint Commission on Government Relations).
4. Assembly exploration of ways of giving greater representation to public sector psychiatrists in the Assembly (Assembly Committee on Public Psychiatry).

The Assembly approved the consortium's recommendation that all district branches be encouraged to include representation of public psychiatry on their executive councils.

Under further study by the council and consortium are the following.

1. APA leadership in developing a national consortium of provider and consumer groups that could, in the public sector context, further interdisciplinary collaboration in care delivery, develop greater collaboration with consumer groups, explore remedies for present deficiencies in public psychiatric services, improve access to care, and explore options for formulation of a national health care plan.
2. APA encouragement of state and other organized mental health agencies to adopt standards of practice for psychiatrists.
3. APA encouragement of state agencies to provide an opportunity for public psychiatrists to spend some time in academic settings in exchange for trainee supervision or other service.

The *Committee on Private Practice,* Boris Rifkin, M.D., chairperson, has stated that its highest priority is survival of the private practitioner. The committee and council appreciate the frustration and confusion faced particularly by the solo office practitioner wrestling with changing practice patterns generated by managed care, Medicare regulations, codes and reimbursement procedures, and the anticipated physician payment scale that will emerge from work on the resource-based relative value scale. Like "public psychiatry," "private practice" has a definition that varies according to context, and clarification of types of practices in the "private practice sector" is needed. Much of the work of the APA components and offices has an impact on the private practitioner—for example, on reimbursement, diagnostic clarification, reviews of various types of treatment, educational programs—but the relationship is not always easily recognized. Many private practitioners do not feel they have a strong voice in the deliberations of the Association. The council and committee are seeking ways to increase the visibility of the Association's commitment to private practitioners, to ensure greater private practice input to relevant APA components, and to organize reporting mechanisms and linkages in such a way as to ensure greater communication with private practitioners. The committee is studying the feasibility of developing a network with private practitioners in the district branches that would expand on the district branch private practice round-table that the committee has sponsored at the annual meeting for the past several years. Several proposals for change in the reporting structure for the committee and for linking the committee to other APA components have been discussed, and the council expects resolution in the coming year.

The *Committee on the Practice of Psychotherapy,* Marcia Goin, M.D., chairperson, looks forward to the National Institute of Mental Health workshop on cost-effectiveness of psychotherapy, which will take place during the spring of 1992. It participated in reviews of initial drafts of practice guidelines for eating disorders and anticipates having an opportunity to be continually involved in the review process. After reviewing summaries of industry-sponsored symposia presented at the 1991 annual meeting, the committee expressed concern that the programs rarely include discussion of psychodynamic psychotherapy as one of the treatment options for the topics presented (anxiety disorders, anxiety and the medically ill, etc.). The committee urged that APA require more scientific balance in these presentations and that the Scientific Program Committee maintain vigilance in this area.

The *Committee on the Chronically Mentally Ill,* Stephen Goldfinger, M.D., chairperson, made known its hope and support for a strong mental health focus within the new Alcohol, Drug Abuse, and Mental Health Services Administration, which will emerge from reorganization as the National Institute of Mental Health, National Institute on Drug Abuse, and National Institute on Alcohol Abuse and Alcoholism are moved under the auspices of the National Institutes of Health. The committee has continued to analyze data from the most recent APA biographical survey to capture information concerning the treatment of the chronically mentally ill. A report is anticipated during 1992. The committee is active in the consortium on public psychiatry, and many of the committee's views are reflected in the recommendations of the consortium.

The long-standing *Committee on Rehabilitation* and the *Task Force on Social Security Income and Social Security Disability Insurance,* both chaired by Arthur T. Meyerson, M.D., were disbanded during 1991. In recent years, the Committee on Rehabilitation wrestled with cuts in funding for treatment of adults with disabilities and the rewriting of the Social Security Administration's disability "listings" for adults and, separately, for children. The group addressed the availability of Medicare for psychiatric patients in nursing homes and addressed administrative cuts in day hospital programs for Medicare recipients by the Health Care Financing Administration. The new *Committee on Psychiatric Disability and Rehabilitation,* with a charge combining aspects of the two former components, is chaired by Kenneth Terkelsen, M.D. The new committee will address matters of national law and regulations affecting children and adults with disabilities, including physical disabilities complicated by psychiatric conditions. The committee will also monitor such matters as guidelines for provision of day treatment and other forms of rehabilitation services provided by psychiatrists. It will promote educational opportunities for psychiatrists in this area.

The *Committee on Psychiatric Services for Mentally Retarded and Developmentally Disabled Persons,* Ludwik S. Szymanski, M.D., chairperson, began its work this year on the shoulders of the previous Task Force on Psychiatric Services to Mentally Retarded Adults. That task force produced a report on the status of psychiatric services to mentally retarded adults and a series of recommendations concerning training, services of state departments of mental health and mental retardation, legislation and regulations, standards, and future areas of focus for APA. The initial plan of the new committee includes development of curricula, networking with a variety of organizations concerned with standards, emerging legislation and regulations, and education. It also hopes to maintain contact with the state departments of mental health and/or mental retardation.

The *Committee on Psychiatric Services in Jails and Prisons,* Henry C. Weinstein, M.D., chairperson, considered ways to increase attention to psychiatric services provided in these settings. The committee will encourage district branches to include representation of the corrections psychiatry field in their public psychiatry components. The committee is exploring the feasibility of a resource pool of individual experts, as well as materials that can be made available to psychiatrists, other interested professionals, and the public.

The *Committee on State and Community Psychiatry Systems,* Steven E. Katz, M.D., chairperson, continued to encourage APA district branches and areas to involve themselves in their states' efforts to develop annual comprehensive plans for psychiatric services in accordance with PL 99-660. State mental health systems are increasingly identifying children and adults with severe mental illnesses as their primary target population. Fewer than one-half of the states currently have full-time medical directors; only seven states require this position by law. The committee developed a job description for medical/clinical directors in state mental health authorities and hopes the description will assist state societies and district branches in persuading their states of the need for such positions. Noting the success of the State-University Collaboration Project, a program aimed at development of collaboration between academic and state psychiatric systems, the committee urged APA to ensure continuation of aspects of this project after the initial 3 years, funded by the Pew Memorial Trust, are completed. Along with the Committee on the Chronically Mentally Ill and others, this committee supported APA efforts to bring about the "unbundling" of the distribution and monitoring of use of clozapine by a single source. More recently, the committee has urged APA to press for financial support through state and federal programs to make clozapine available to those who will benefit from it.

The *Committee on Psychiatric Services in the Military,* Harry C. Holloway, M.D., chairperson, called to the attention of the council the development of mental health standards by the Department of Defense's Office of Health Affairs and prompted APA to offer expertise and advice. Many members of the committee were intensely involved in delivery of psychiatric services during and after Operation Desert Shield/Storm. They reminded the council that while the military effort in the Middle East is ostensibly over, the problems of military personnel and their families, including those of reserves, will continue to surface for some time. The committee hopes for psychiatry's continued interest in and willingness to assist military personnel and their families. Working with APA's Division of Government Relations, the committee provided valuable advice concerning CHAMPUS, the downsizing of the military force and military medicine, the Department of Defense pilot program for training psychologists to prescribe medications, and military and Public Health Service pay issues.

The *Committee on Veterans' Affairs,* Frederick Guggenheim, M.D., alerted the council that as Congress considers universal access to care, only one current plan mentions use of Department of Veterans Affairs (VA) hospitals. The committee urged the association to keep in mind how the VA system, particularly specialty care, can fit into plans for universal access to care. The committee monitored and commented on a number of reports of national significance, including two from the Institute of Medicine concerning research and use of resources and one from the VA Mission Commission, a federal commission studying the future structure of veterans' health care systems. The committee provides advice to the Division on Government Relations concerning education, budget, and pay issues, and in September the members of the committee conducted continued their annual visits to members of Congress.

The *Committee on the H&CP Service,* Gail Barton, M.D., chairperson, reaffirmed its commitment to serve mental health professionals in its 800-plus member facilities, as well as its commitment to distributing nearly 10,000 copies of *Hospital and Community Psychiatry* to professionals in those facilities. For 1992 the committee supports further expansion of the video and film library, which now includes more than 150 titles. Reviews and selection of videos included in this unique collection are made by Ian E. Alger, M.D. The 1992 "Video and Film Library Catalog," listing all the videos available for rent from the H&CP Service, is available on request. The Psychiatric Placement Service, established by the H&CP Service to help hospitals and other facilities find psychiatrists for vacant positions, receives continued support from the committee and staff. Since the program was established in 1986, 72 psychiatrists have found new positions through this program.

The *Institute on Hospital and Community Psychiatry Program Committee,* Harold Eist, M.D., chairperson, continued its practice of current, practical, interactive sessions at its meeting in Los Angeles on Oct. 20–24, 1991. The institute's theme, "Overcoming Challenges With Diversity," was reflected in a vast range of topics, such as psychopharmacology, gang violence, managed care, sexual harassment, borderline disorders, and insomnia. Seventeen professional groups held meetings in conjunction with the institute, including the Pacific Rim College of Psychiatrists, which held a 3-day meeting before the institute. Dr. Eist chaired "The Experience of a Heart Attack: Medical and Psychiatric Perspectives," for which a faculty of a cardiologist and psychiatrists came together to discuss these issues around a "love-your-heart" luncheon. David O. Olenik, M.D., is chairperson of the program committee for the 1992 H&CP institute, which will be held in Toronto on Oct. 23–27.

The *Task Force on the Homeless Mentally Ill,* Frederic I. Kass, M.D., chairperson, published its second interim report, "Homeless Families and Children: A Psychiatric Perspective." This report and the 1990 report "General Directions for Public Policy in Behalf of the Mentally Ill Among the Homeless Population" are available on request from the APA Office of Psychiatric Services. The task force completed a book that includes recommendations and a summary of developments in psychiatric services for the homeless mentally ill in the last several years. The task force has initiated workshops for district branches at the last two APA annual meetings, with the goal of facilitating exchange of information, know-how, and enthusiasm among district branches interested in developing local programs for the homeless mentally ill population.

The *Task Force on Family/Systems Therapy,* Fred Gottlieb, M.D., chairperson, created linkages to other APA components, raising consciousness about family/systems therapy in terms of considerations for treatment, reimbursement, and education. The task force has reviewed previously published APA documents on the topic and has developed a framework for approaching current issues that encompass definitions, considerations for treatment, education, practices (including the possibility of practice guidelines), third-party payment issues (including coding and reimbursement), and research.

The *Task Force on Clinician Safety,* William Dubin, M.D., chairperson, refined its report. It is anticipated that the report will be recommended for publication in 1992. The task force continued its study of the issues, including facilitation of a milieu that would minimize violence, threats, and assaults in forensic hospitals and involvement of legal authorities in threats.

The *Committee on Liaison With the American Hospital Association,* Stuart Keill, M.D., chairperson, in concert with its counterpart committee at the American Hospital Association, recommended that the joint committee of the two associations be disbanded. To ensure ongoing liaison and communication, and on the recommendation of the council, the boards of both APA and the American Hospital Association agreed that a representative and staff person of the American Hospital Association would serve as consultants to several APA councils and that an APA representative and staff person would participate in the American Hospital Association's Governing Council on Psychiatric and Substance Abuse Services. Both organizations encourage appointment of members representing the interests of psychiatry and hospitals on key policy development committees critical to concerns of both organizations. Throughout the 30 years of its existence, the joint committee promoted cooperation between the two organizations on programs, positions, and legislative and regulatory matters.

It has been a busy and rewarding year. The council anticipates several challenges in the coming year relating to access to services, quality of care, and the strength of psychiatry's contribution in the many areas that touch on treatment and services.

# The Council on Psychiatry and Law

## Paul Appelbaum, M.D., Chairperson

In December of 1989, the APA Board of Trustees approved a resource document proposed by the council concerning patients' right to refuse medication. The document was approved with the proviso that the council would review the experiences of states that had mandated judicial review for refusals of medication in order to understand the problems and any possible benefits. After studying a survey of the states that require judicial review of involuntary treatment decisions, the council agreed to prepare a supplement to the resource document on the right to refuse medication that would focus on the disadvantages and advantages of judicial review systems. The supplemental paper, which also includes model guidelines for improving the efficiency of the judicial model, has been completed, was approved by the Joint Reference Committee in October 1991, and will be forwarded to the Assembly of District Branches in November.

The council has continued examining psychiatrists' responsibility for reporting impaired driving by mentally ill persons to departments of motor vehicles. Council member Jeffrey Metzner, M.D., chaired a task force of the Federal Highway Administration that examined commercial driving permits for people suffering psychiatric diseases or disorders. Dr. Metzner shared the final report of the task force with council members at the council's fall meeting. A representative of the Council on Aging joined the council during the fall meeting for its discussion. The Council on Psychiatry and Law and the Council on Aging will appoint a working group to explore this issue further, specifically to determine what psychiatrists know about the impacts of various disorders and medications on driving capacity and what sorts of responsibilities psychiatrists should have. The initial focus of the subcommittee will be the effect of dementia on the driving capacity of older persons.

The council met with the chairperson of the Committee on Women to discuss laws designed to control patient-therapist sexual contact. States have adopted a variety of statutory approaches to the problem of sexual relationships between patients and therapists. Basically, the three approaches states are taking in legislation are l) statutes to make civil suits easier, e.g., by increasing statutes of limitations or shielding complainants from questions about prior sexual activity, 2) statutes criminalizing sexual misconduct by physicians, and 3) statutes regulating the reporting of sexual misconduct by physicians. At its October meeting, the Joint Reference Committee instructed the council to develop, in conjunction with the Committee on Women, model legislation for use by the district branches. A working group has been established for this purpose and will report to the council in May.

The council, in conjunction with the Commission on Judicial Action, has been exploring peer review of expert testimony. As a result of this exploration, the council believes that peer review may be a useful mechanism for improving the quality of psychiatrists' performance in court. Further, the council believes that as experience with and knowledge about peer review grows, it is likely that models serving the ultimate end of increasing the quality of expert testimony will develop. The council has drafted a proposed position statement on peer review of expert testimony and a proposed resource document on peer review of psychiatric expert testimony, which may assist groups that are interested in developing peer review mechanisms. Both of these documents were approved by the Joint Reference Committee and will be referred to the Assembly of District Branches (the position statement for approval, the resource document for review) at its November meeting. The council hopes both documents will be approved by the Board of Trustees at its December meeting. Additionally, the council feels that a task force on peer review of psychiatric expert testimony should be established to further study this issue and to develop mechanisms for implementation of peer review programs. The American Academy of Psychiatry and Law has agreed to collaborate in the work of this task force. The Joint Reference Committee has recommended that the Board of Trustees approve the establishment of this task force.

The council also has been working with the Joint Commission on Government Relations and the Division of Government Relations in dealing with such issues as guardianship and advance directives for psychiatric treatment.

The *Committee on Confidentiality,* Renee L. Binder, M.D., chairperson, has established a column in *Psychiatric News* that addresses current confidentiality topics in a question-and-answer format. The committee is currently exploring the development of a new confidentiality videotape, the issue of confidentiality and technology, and confidentiality issues raised by managed care.

The *Task Force on Disclosure of Psychiatric Treatment Records in Child Custody Disputes,* Carl Malmquist, M.D., chairperson, has completed its charge. The task force report, "Disclosure of Psychiatric Treatment Records in Child Custody Disputes," has been approved by the Board of Trustees, and publication is expected in mid to late November. This report points out that judicial decisions concerning disclosure in custody proceedings of information obtained during psychiatric treatment often neglect harms that may result from such disclosure. The report recommends directing courts to order that information revealed in psychiatric treatment be disclosed in custody proceedings only when one disputant offers substantive evidence that the parent who has received psychiatric treatment is currently unable to provide adequate care for the child and when the information sought is likely to support this allegation.

The *Task Force on Use and Misuse of Psychiatric Diagnoses in the Courts,* Seymour Halleck, M.D., chairperson, has completed its report. The Joint Reference Committee has approved the draft and referred the report to the Board of Trustees for approval. The document will be reviewed by the Assembly of District Branches at its November meeting. The legal system has increasingly called on psychiatrists to help resolve legal conflicts, and the report aims to clarify legitimate uses of diagnoses in legal adjudication and their limitations. Additionally, the council has been working closely with the Task Force on DSM-IV to address the ways in which the complicated questions involved in legal uses of *DSM-IV* could be addressed.

The *Task Force on Consent to Voluntary Hospitalization,* Francine Cournos, M.D., chairperson, hopes to have a final draft of its report for review by the council at its May meeting. This report will focus on the issues involved in *Zinermon v. Burch.* This case raised questions about the legitimacy of consent given by patients who may be incompetent at the time of voluntary hospitalization and suggested that those patients should be dealt with by involuntary commitment.

# The Council on Research

Herbert Pardes, M.D., Chairperson

The Council on Research, in conjunction with its components, is the body within the Association that ensures the vigor of the psychiatric research enterprise by focusing on science policy and scientific assessment issues, research studies, and, especially important, research training issues. The council has been carefully monitoring science policy issues, particularly those concerned with animal research, research appropriations,conflict of interest issues, training and infrastructure needs, and child psychiatry research funding. Many of these issues and those of the research components are addressed in the column "News From the Council on Research" in *Psychiatric Research Report (PRR),* the Office of Research quarterly newsletter. Individuals who would like to receive *PRR* should contact the APA Office of Research.

The council was delighted to meet and continue its annual discussions with key leaders of the federal research agencies, including the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Drug Abuse (NIDA). Over the years these meetings have provided an opportunity for informal collaboration and have identified issues of mutual concern. This year's discussions focused largely on the reorganization of ADAMHA. Under the proposed reorganization (which had not received legislative approval at the time of this writing), the research programs of NIMH, NIDA, and NIAAA would be administratively housed within the National Institutes of Health (NIH). Service and prevention programs would remain with ADAMHA, which would be renamed the Alcohol, Drug Abuse, and Mental Health Services Administration (ADAMHSA). The council voiced concern about the reorganization's potential effect on the successful coalition of groups supporting the three institutes. Other topics addressed with the agencies included the psychiatric research infrastructure, research competitiveness in departments of psychiatry, and research appropriations.

The council collaborated with the APA Division of Government Relations and the Joint Commission on Government Relations on a number of important issues. The council was particularly concerned with legislation that would cap indirect costs at 26% for ADAMHA and NIH federal grants. In addition, the council is asking that APA formally advocate a loan forgiveness program for psychiatric research trainees and that the Division of Government Relations assist with the implementation of this policy.

The council administers two APA awards—the Lilly Psychiatric Research Fellowship and the Kempf Fund Award for Research Development in Psychobiological Psychiatry. The council appointed Ronald Rieder, M.D., Judith Rapoport, M.D., Robert Hirschfeld, M.D., and Walter Hong, M.D., to review the 1992 applications and select the winners. The winners of the 1991 Kempf award were David L. Braff, M.D. (senior awardee) and Neal R. Swerdlow, M.D. (junior awardee). Robert T. Malison, M.D., received the Lilly Psychiatric Research Fellowship.

Following are details of the activities of components under the Council on Research.

The final report of the *Task Force on Tardive Dyskinesia,* John Kane, M.D., chairperson, was approved by the Board of Trustees in December 1990 and is to be published in December 1991 (1). The final report of the *Task Force on Quantitative Electrophysiological Assessment,* Robert Freedman, M.D., chairperson, was also approved by the Board of Trustees in December 1990 and was published in July 1991 (2). The council thanked both task forces for their important contributions to the literature and recommended to the Board that they be disbanded.

The *Committee on Research on Psychiatric Treatments,* John Kane, M.D., chairperson, continues to assess and respond to scientific issues regarding psychiatric treatment (for example, a possible relationship between antidepressants and suicide). In conjunction with the Council on Addiction Psychiatry, the committee has recommended the establishment of a task force on nicotine dependence to address this important public health issue. If approved by the Board of Trustees, the task force would be charged with educating psychiatrists regarding the seriousness of nicotine addiction and the need for treatment, assessing current scientific information in the field, identifying reimbursement issues, developing recommendations for training, establishing a general research agenda, and developing a position paper.

The committee has also met with a representative of the U.S. Food and Drug Administration (FDA) and with a representative of NIMH regarding the development of a treatment research branch of NIMH. It continues to review APA's efforts to develop practice guidelines and to monitor issues involving clozapine and anticonvulsant drugs.

Further, the Committee on Research on Psychiatric Treatments oversees treatment-related task forces, including the Task Force on Electroconvulsive Therapy and the Task Force on Psychosocial Treatment Research. Summaries of their activities follow.

The *Task Force on Electroconvulsive Therapy,* Richard Weiner, M.D., Ph.D., chairperson, continues to monitor proposed regulations published by the FDA to reclassify ECT devices from class III (requiring premarket approval) to class II (requiring a performance standard) for use in treating severe depression. The task force, working in conjunction with the Division of Government Relations and coordinating its activities with those of other groups and individual psychiatrists, hopes to modify the regulations to include mania and schizophrenia in this reclassification and to clarify the meaning of "severe depression."

The *Task Force on Psychosocial Treatment Research,* John Docherty, M.D., chairperson, submitted a draft of its final report. The document was approved by the Committee on Research on Psychiatric Treatments in May 1991 and by the Council on Research in September 1991. It was forwarded to the Joint Reference Committee, and that body returned it to the council for modification.

The *Steering Committee on Practice Guidelines,* John S. McIntyre, M.D., chairperson, has been establishing the process for developing practice guidelines for psychiatrists. It has outlined a standardized method to ensure that the final products are based on well-documented evidence, have substantial clinician input, and are widely reviewed. A variety of dissemination strategies are under consideration. Guidelines in four areas have been drafted by distinct work groups, with input from a wide range of individuals, and are presently in varying stages of completeness. The four areas are eating disorders, major depression, adult outpatient evaluation, and adult inpatient evaluation. Future guideline topics under consideration include schizophrenia, evaluation and management of mental disorders in the geriatric population, and bipolar disorder. Steering committee members and staff continue active liaison with organizations and agencies involved in various aspects of practice guidelines development. In addition, a program for achieving more sophisticated approaches to developing practice guidelines was recently funded by NIMH.

The *Committee on Research Training,* Ron Rieder, M.D., chairperson, continues to focus on the recruitment and development of psychiatric researchers. The committee is attempting to generate support for research by medical students during the summer in departments of psychiatry and is developing a report on women in research. Mentorship is another focus; the committee has proposed a workshop on research mentoring for the 1992 annual meeting, after the success of the 1991 workshop on overcoming obstacles to starting research. In September 1991 the committee developed the "Guide for Residents and Fellows Seeking Research Training Opportunities," which is designed to help trainees ask questions about and evaluate the available opportunities for research in various departments of psychiatry. This guide has been distributed through the Psychiatric Research Training Clearinghouse. The committee has suggested that the guide also be included in a second edition of the "Directory of Research Fellowship Opportunities in Psychiatry," the first edition of which was published by the Office of Research in October 1990. This resource includes listings of research fellowship opportunities compiled from responses to a questionnaire about postgraduate research training opportunities that was sent to directors of residency training in November 1989. It also includes introductory material about APA programs and activities, information on research careers, and listings of programs and suggestions on how readers might use them.

The Residency Review Committee for Psychiatry of the Accreditation Council for Graduate Medical Education is developing research requirements for geriatric fellowship programs (the first such research training requirements in a subspecialty). The committee and council are strongly supporting the requirement of a research component in fellowship training. The committee also asked APA to formally request the Residency Review Committee to require that residency training programs have a plan for conducting research that can be offered to residents interested in research. This recommendation was approved by the Joint Reference Committee in September 1991 and referred to the Board of Trustees for consideration in December.

The *Committee on the Biographical Directory and Research on Psychiatric Professional Activities,* Robert Dorwart, M.D., chairperson, is exploring a number of publication options for future directories and will present several to the council for its consideration next spring. Specifically, the committee believes that a smaller, less costly, more timely directory may be needed. Most research data would then be collected through smaller, specifically targeted sample surveys separate from the directory process. The committee is working with the Offices of Research and Membership, the Council on Research, and the Committee on Membership to further develop these plans.

The committee continues to analyze the data collected from the Professional Activities Survey and has provided data to the Committee on the Chronically Mentally Ill and to the Task Force on Psychiatrist Payment for the study of specific topics. The committee is also writing an article describing basic survey findings for publication in an APA journal, and it is working collaboratively with researchers at Harvard University, Johns Hopkins University, and the University of Arkansas to rapidly analyze and disseminate survey findings on policy issues that are important to APA and the field.

The *Committee on Psychiatric Diagnosis and Assessment,* Layton McCurdy, M.D., chairperson, oversees diagnostic assessment activities, including the work of the Task Force on DSM-IV (separate report follows). In addition to overseeing this important component, the committee has considered the linkages between *DSM-IV* and *ICD-10,* the implications of the profusion of suggestions for new *DSM* diagnoses, and coordination between *DSM* efforts and education and forensic issues. The committee has also been seeking to further communication between psychiatrists interested in neurophysiological assessment techniques and the American Board of Psychiatry and Neurology, which recently developed a program for added qualification for psychiatrists and neurologists in this area.

The *Task Force on DSM-IV,* Allen Frances, M.D., chairperson, has completed work on the *DSM-IV Options Book* (3), a comprehensive listing of issues identified in the process of developing *DSM-IV* and options for their resolution. Data collection has continued over the last year through NIMH-focused field trials. Results from the field trials, as well as data reanalysis funded by the John D. and Catherine T. McArthur Foundation, will be available by May 1992 and will help the task force make final decisions about specific diagnostic categories in *DSM-IV.* The task force is also supervising the efforts of the DSM-IV Primary Care Work Group, which has begun some preliminary work on a primary care version of *DSM-IV.* The task force edits bimonthly columns on *DSM-IV* in *Hospital & Community Psychiatry* and produces *DSM-IV Update,* a semiannual newsletter. Individuals wishing to receive copies of *DSM-IV Update* should write to the APA Office of Research.

The *Task Force on Traumatic Brain Injury,* Stuart Yudofsky, M.D., chairperson, was established in 1990 and reports directly to the Council on Research. It is focusing its efforts on the education of physicians through the development of a model curriculum for medical students and residents, liaison with other medical societies (i.e., pediatricians, family practitioners, and internists), and presentations on the psychiatric aspects of traumatic brain injury to other medical societies. The task force also plans to develop an informational brochure for victims of traumatic brain injury and their families. The task force presented a very successful workshop at the 1991 annual meeting and hopes to organize a symposium for the 1992 annual meeting in Washington, D.C.

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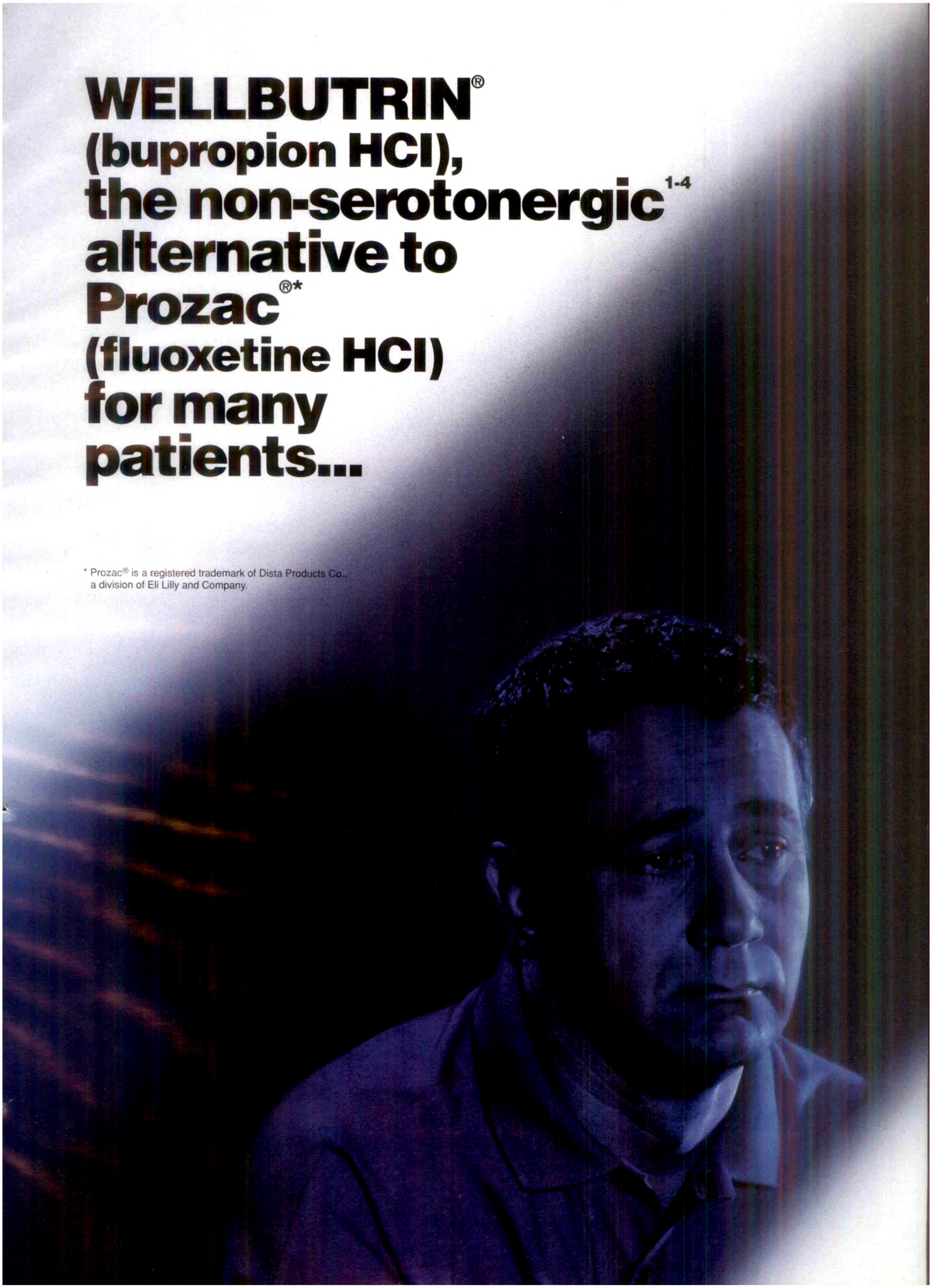

**WELLBUTRIN®**
**(bupropion HCl),**
**the non-serotonergic[1-4]**
**alternative to**
**Prozac®***
**(fluoxetine HCl)**
**for many**
**patients...**

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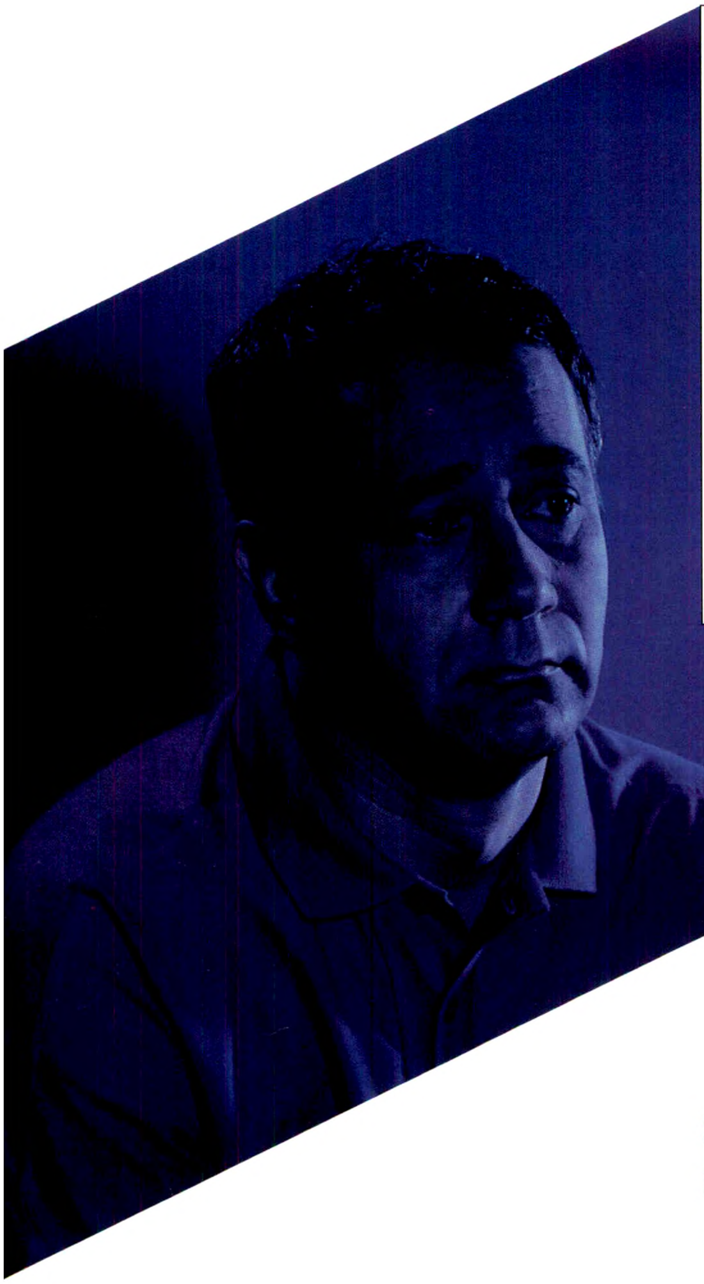
* Prozac® is a registered trademark of Dista Products Co., a division of Eli Lilly and Company.

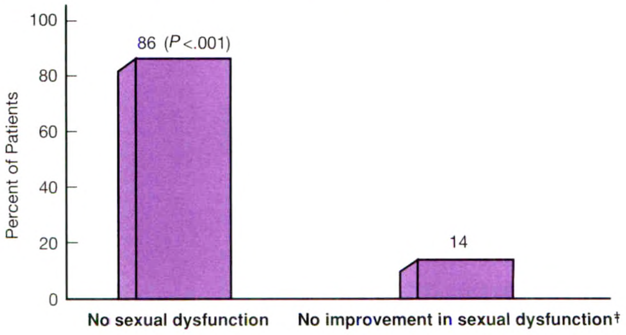
# Bill's doctor wants a new-generation antidepressant that minimizes risk of sexual dysfunction but is non-serotonergic.

■ Because WELLBUTRIN may cause little sexual dysfunction, it may improve patient compliance.[5]



**Relieves depression with fewer adverse effects on sexual performance**

Male Patients Switched to WELLBUTRIN Who During Previous Antidepressant Therapy* Experienced Sexual Dysfunction (N=28)[5]†



*Including tricyclics, MAO inhibitors, maprotiline, and trazodone.

**Start with non-serotonergic**

# Wellbutrin®

(BUPROPION HCl)

**Relieves depression with few life-style disruptions**

†Impairments that ceased to occur after treatment with WELLBUTRIN were decreased libido, decreased erectile capacity, or delayed or retrograde ejaculation.

‡Of the four patients (age range: 50 to 67) who demonstrated no change in sexual dysfunction, two were diabetic and two had lifelong histories of sexual disability.

# The man whose medication caused sexual dysfunction

Name: Bill – Occupation: Unemployed administrative assistant
Age: 48 – Height: 5'10" – Weight: 170 lb

**History**
Patient complains of fatigue, inability to concentrate, and feelings of worthlessness since staff cuts at the corporation where he worked for 21 years resulted in the loss of his job. He has failed to begin company-sponsored job retraining program and to look for a new job.

**Diagnosis: Depression**

**Initial treatment**
After 2 months of antidepressant treatment, patient complains of sexual dysfunction (erectile failure and decreased libido), which had not been a problem prior to antidepressant treatment. Although patient's depression has improved, he insists the medication is causing the sexual dysfunction and requests that medication be discontinued.

**Recommendation**
Discontinue current antidepressant and switch to a new-generation, non-serotonergic antidepressant. Start WELLBUTRIN to relieve depression and minimize risk of sexual dysfunction.

**Outcome**
After 4 weeks of therapy with WELLBUTRIN, patient reports feeling more energetic.
Sexual performance is normal.
He has enrolled in job retraining program.

*See brief summary of full prescribing information on last page of this advertisement.*

# Start with WELLBUTRIN, the non-serotonergic alternative to Prozac®* (fluoxetine HCl) for many patients.

## As a new-generation antidepressant, WELLBUTRIN offers:

- Effective relief of depression with few life-style disruptions
- Few cardiovascular effects[6-8]
- Few anticholinergic effects[3,9]
- Little or no weight gain[3,10]
- Little or no daytime drowsiness[9]
- Minimal risk of sexual dysfunction[5]

The principal medically important adverse reaction with WELLBUTRIN is seizure, which occurs in approximately four-tenths of one percent of patients. This incidence may exceed that of other marketed antidepressants, although no direct comparative studies have been conducted. For more information about dosing to achieve optimal patient response and recommendations for reducing the risk of side effects, see full prescribing information, especially the DOSAGE AND ADMINISTRATION and WARNINGS sections.

**References:**

**1.** Shea VK, Wang CM. Bupropion (Wellbutrin®) inhibits the firing rates of noradrenergic but not serotonergic neurons. *Soc Neurosci.* 1985;2:185. Abstract. **2.** Ferris RM, Cooper BR, Maxwell RA. Studies of bupropion's mechanism of antidepressant activity. *J Clin Psychiatry.* 1983;44(5, sec 2):74-78. **3.** Data on file, Burroughs Wellcome Co., 1991. **4.** Richelson E. Synaptic pharmacology of antidepressants: an update. *McLean Hosp J.* 1988;13:67-88. **5.** Gardner EA, Johnston JA. Bupropion—an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol.* 1985;5:24-29. **6.** Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44(5, sec 2):170-173. **7.** Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987;7:247-251. **8.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **9.** Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry.* 1990;51:194-199. **10.** Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. Effects of bupropion on body weight. *J Clin Psychiatry.* 1983;44(5, sec 2):183-186.

The patient depicted in this advertisement is not an actual patient, but is a fictional composite of typical patient types.

*See brief summary of full prescribing information on last page of this advertisement.*

* Prozac® is a registered trademark of Dista Products Co., a division of Eli Lilly and Company.

Wellcome

**Burroughs Wellcome Co.**
Research Triangle Park, NC 27709

**Start with non-serotonergic**

**Wellbutrin®**

(BUPROPION HCl)

**Relieves depression with few life-style disruptions**

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Printed in U.S.A. WB-Y02160 February 1991

# WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

**Before prescribing, please consult complete product information, a summary of which follows:**
**INDICATIONS AND USAGE:** Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.
**CONTRAINDICATIONS:** Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin
**WARNINGS: SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.**
**During the initial development, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).**
**A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.**
**The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.**
***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose not to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**
**Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.
**PRECAUTIONS: General:**
***Agitation and Insomnia:*** A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.
***Psychosis, Confusion, and Other Neuropsychiatric Phenomena:*** Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.
***Activation of Psychosis and/or Mania:*** Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.
***Altered Appetite and Weight:*** A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.
***Suicide:*** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.
**Use in Patients with Systemic Illness:** There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.
Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.
**Information for Patients:** Consult complete product information.
**Drug Interactions:** No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.
However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.
Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).
Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).
Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.
Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.
**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.
Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.
A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.
**Pregnancy: *Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
**Labor and Delivery:** The effect of Wellbutrin on labor and delivery in humans is unknown.
**Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of Wellbutrin in individuals [illegible] established.
**Use in the Elderly:** Wellbutrin has not been systematically evaluated [illegible]
**ADVERSE REACTIONS:** (See also WARNINGS and PRECAUTIONS [illegible] in patients treated with Wellbutrin are agitation, dry mouth, insomnia [illegible] constipation, and tremor.
Adverse events were sufficiently troublesome to cause discontinu[illegible] approximately ten percent of the 2400 patients and volunteers who [illegible] product's initial development. The more common events causing disco[illegible] disturbances (3.0%), primarily agitation and abnormalities in mental sta[illegible] (2.1%), primarily nausea and vomiting; neurological disturbances (1.7[illegible] sleep disturbances; and dermatologic problems (1.4%), primarily ra[illegible] that many of these events occurred at doses that exceed the recom[illegible]
The table below is presented solely to indicate the relative frequ[illegible] representative controlled clinical studies conducted to evaluate t[illegible] under relatively similar conditions of daily dosage (300-600 mg), setting [illegible] cited cannot be used to predict precisely the incidence of untoward [illegible] practice where patient characteristics and other factors must diffe[illegible] clinical trials. These incidence figures also cannot be compared with the [illegible] involving related drug products as each group of drug trials is conducted [illegible] Finally, it is important to emphasize that the tabulation does not ref[illegible] importance of the events. A better perspective on the serious adverse events [illegible] is provided in the WARNINGS and PRECAUTIONS sections.

**TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CO[illegible]**
**(Percent of Patients Reporting)**

| Adverse Experience | Wellbutrin Patients (n = 323) | Placebo Patients (n = 185) |
|---|---|---|
| CARDIOVASCULAR | | |
| Cardiac Arrhythmias | 5.3 | 4.3 |
| Dizziness | 22.3 | 16.2 |
| Hypertension | 4.3 | 1.6 |
| Hypotension | 2.5 | 2.2 |
| Palpitations | 3.7 | 2.2 |
| Syncope | 1.2 | 0.5 |
| Tachycardia | 10.8 | 8.6 |
| DERMATOLOGIC | | |
| Pruritus | 2.2 | 0.0 |
| Rash | 8.0 | 6.5 |
| GASTROINTESTINAL | | |
| Anorexia | 18.3 | 18.4 |
| Appetite Increase | 3.7 | 2.2 |
| Constipation | 26.0 | 17.3 |
| Diarrhea | 6.8 | 8.6 |
| Dyspepsia | 3.1 | 2.2 |
| Nausea/Vomiting | 22.9 | 18.9 |
| Weight Gain | 13.6 | 22.7 |
| Weight Loss | 23.2 | 23.2 |
| GENITOURINARY | | |
| Impotence | 3.4 | 3.1 |
| Menstrual Complaints | 4.7 | [illegible] |
| Urinary Frequency | 2.5 | 2.2 |
| Urinary Retention | 1.9 | 2.2 |
| MUSCULOSKELETAL | | |
| Arthritis | 3.1 | 2.7 |
| NEUROLOGICAL | | |
| Akathisia | 1.5 | 1.1 |
| Akinesia/Bradykinesia | 8.0 | 8.6 |
| Cutaneous Temperature Disturbance | 1.9 | 1.6 |

| Adverse Experience | [illegible] | [illegible] |
|---|---|---|
| Dry Mouth | [illegible] | [illegible] |
| Excessive Sweating | [illegible] | [illegible] |
| Headache/Migraine | [illegible] | [illegible] |
| Impaired Sleep Quality | [illegible] | [illegible] |
| Increased Salivary Flow | [illegible] | [illegible] |
| Insomnia | [illegible] | [illegible] |
| Muscle Spasms | [illegible] | [illegible] |
| Pseudoparkinsonism | [illegible] | [illegible] |
| Sedation | [illegible] | [illegible] |
| Sensory Disturbance | [illegible] | [illegible] |
| Tremor | [illegible] | [illegible] |
| NEUROPSYCHIATRIC | | |
| Agitation | [illegible] | [illegible] |
| Anxiety | [illegible] | [illegible] |
| Confusion | [illegible] | [illegible] |
| Decreased Libido | [illegible] | [illegible] |
| Delusions | [illegible] | [illegible] |
| Disturbed Concentration | [illegible] | [illegible] |
| Euphoria | [illegible] | [illegible] |
| Hostility | [illegible] | [illegible] |
| NONSPECIFIC | | |
| Fatigue | [illegible] | [illegible] |
| Fever/Chills | [illegible] | [illegible] |
| RESPIRATORY | | |
| Upper Respiratory Complaints | [illegible] | [illegible] |
| SPECIAL SENSES | | |
| Auditory Disturbance | [illegible] | [illegible] |
| Blurred Vision | [illegible] | [illegible] |
| Gustatory Disturbance | [illegible] | [illegible] |

*Events reported by at least 1% of Wellbutrin patients are included.

**Other Events Observed During the Development of Wellbutrin:** [illegible] exposure to Wellbutrin varied greatly and a substantial proportion of the experien[illegible] uncontrolled clinical settings. During this experience, numerous adverse e[illegible] without appropriate controls, it is impossible to determine with certainty which eve[illegible] by Wellbutrin. The following enumeration is organized by organ system and desc[illegible] relative frequency of reporting in the data base. Events of major clinical import[illegible] the WARNINGS and PRECAUTIONS sections of the labeling.
The following definitions of frequency are used: Frequent adverse events are [illegible] at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 t[illegible] events are those occurring in less than 1/1000 patients.
***Cardiovascular:*** Frequent was edema; infrequent were chest pain, EKG abnor[illegible] and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were [illegible] myocardial infarction.
***Dermatologic:*** Frequent were nonspecific rashes; infrequent were alopecia [illegible] change in hair color, hirsutism and acne.
***Endocrine:*** Infrequent was gynecomastia; rare were glycosuria and hormo[illegible]
***Gastrointestinal:*** Infrequent were dysphagia, thirst disturbance, and liver damage [illegible] complaints, colitis, G.I. bleeding, intestinal perforation and stomach ulcer
***Genitourinary:*** Frequent was nocturia; infrequent were vaginal irritation, testicu[illegible] infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary [illegible] ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation
***Hematologic/Oncologic:*** Rare were lymphadenopathy, anemia and pancytopen[illegible]
***Musculoskeletal:*** Rare was musculoskeletal chest pain
***Neurological:*** (see WARNINGS) Frequent were ataxia/incoordination, seizure, my[illegible] dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were EEG [illegible] neurological exam, impaired attention, sciatica and aphasia.
***Neuropsychiatric:*** (see PRECAUTIONS) Frequent were mania/hypomania, increase[illegible] decrease in sexual function, and depression; infrequent were memory impairment, deperso[illegible] dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare [illegible]
***Oral Complaints:*** Frequent was stomatitis; infrequent were toothache, bruxism, gum [illegible] rare was glossitis.
***Respiratory:*** Infrequent were bronchitis and shortness of breath/dyspnea; rare were [illegible] disorder, pneumonia and pulmonary embolism.
***Special Senses:*** Infrequent was visual disturbance; rare was diplopia.
***Nonspecific:*** Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were [illegible] related pain, infection, medication reaction and overdose.
**Observed During Clinical Practice:** Based on clinical practice experience in patien[illegible] spontaneously reported adverse reactions are uncommon. Data are insufficient to [illegible] their incidence or to establish causation. Voluntary reports of adverse reactions [illegible] since market introduction include:
***Cardiovascular:*** orthostatic hypotension
***Gastrointestinal:*** esophagitis, hepatitis
***Hemic and Lymphatic:*** ecchymosis, leukocytosis, leukopenia
***Musculoskeletal:*** arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis
***Nervous:*** coma, delirium, dream abnormalities, paresthesia, unmasking of tardive [illegible]
***Skin and Appendages:*** angioedema, exfoliative dermatitis, urticaria
***Special Senses:*** tinnitus

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THE AMERICAN JOURNAL OF PSYCHIATRY

# Information for Authors

## GENERAL POLICIES

The requirements stated below are in accordance with the International Committee of Medical Journal Editors. See Uniform Requirements for Manuscripts Submitted to Biomedical Journals, N Engl J Med 1991; 324:424–428.

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### Disclosure of Commercial Interests

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Ethical and legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. Also, authors should disguise identifying information when discussing patients' characteristics and personal history.

### Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

### Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

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Papers may be submitted before the annual meeting, but they cannot be published until after the meeting. They must be accompanied by a statement that they are in final form. These papers receive the same peer review as other papers and must meet the requirements for one of the types of articles specified in the next section. The *Journal* no longer maintains right of first refusal for annual meeting papers.

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These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words, **including** an abstract of no more than 250 words, references, tables, and figures (to determine word equivalence, see section on Tables and Figures). This section is not intended to be a forum for the presentation of new data.

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Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research, containing new data derived from a sizable series of patients. Regular Articles contain no more than 3,800 words, **including** an abstract of no more than 250 words, references, tables, and figures (to determine word equivalence, see section on Tables and Figures).

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All parts of the manuscript or letter to the Editor, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8.5×11 inch **nonerasable** bond paper. All four margins must be 1.5 inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered. The original and four copies of a manuscript, including tables and figures, should be submitted.

## STYLE SPECIFICATIONS

### Title Page

**Title.** The title should be informative and as brief as possible. Two-part titles should be avoided.

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All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data, and (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

Only those with key responsibility for the material in the article should be listed as authors; others contributing to the work should be recognized separately. Editors may require authors to justify the assignment of authorship.

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**Location of work and address for reprints.** Provide the department, institution, city, and state **where the work was done.** Include a full address for the author who is to receive reprint requests.

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## Abstract

Authors of review articles must include the following information, under the headings indicated: Objective—the primary purpose of the review article; Method—data sources, study selection (the number of studies selected for review and how they were selected), data extraction (rules for abstracting data and how they were applied); Results—methods of data synthesis, key findings; and Conclusions—including potential applications and research needs. Authors of research articles must include Objective—questions addressed by the study; Method—design of the study, setting (location and level of clinical care), patients or participants (manner of selection and number who entered and completed the study), interventions (if any), main outcome measures (primary study outcome measure as planned before data collection); Results—key findings; and Conclusions—including direct clinical applications. Other types of articles, including Clinical and Research Reports, should include unstructured abstracts.

The abstract is a single paragraph no longer than 250 words for Special Articles and Regular Articles and no longer than 60 words for Clinical and Research Reports.

## Text

**Research design and statistics.** The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Standard deviations, rather than standard errors of the mean, are required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain (F=4.32, df=3, 17, p<0.05)." Reviewers will evaluate the appropriateness of the analyses.

**Abbreviations.** Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

**Drugs.** Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

## References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

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Type references in the style shown below, **double-spaced throughout. List all authors;** do not use "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, Rifkin A, Rubin RT, Swinson RP, Ballenger JC, Burrows GD: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

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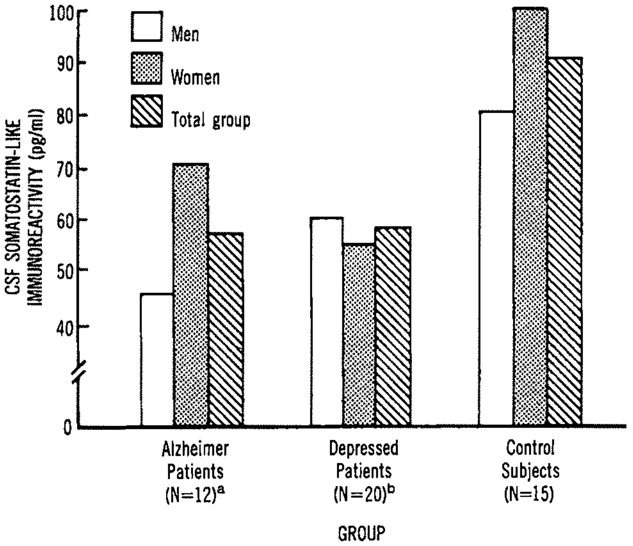
## Tables

**Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines.** Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

**FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects**



[a] Significant difference between men and women (t=1.81, df=10, p<0.05) and between the total Alzheimer's disease group and the total control group (t=2.49, df=25, p<0.01).

[b] Significant difference between the total depressed group and the total control group (t=2.75, df=33, p<0.005).

### Figures

Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. All figure titles and footnotes should be typed and sent together on a separate page.

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2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
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5. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
6. To save space, related figures that have the same vertical or horizontal axis should be combined and identified with internal headings.
7. The key should appear within or above the figure but should not widen the figure. Avoid placing other type (e.g., number of subjects, statistical values) within a graph.
8. Footnotes (including p values) should be cited with superscript letters in the title or in the axis labels and should be listed in the order in which they are cited in the figure.
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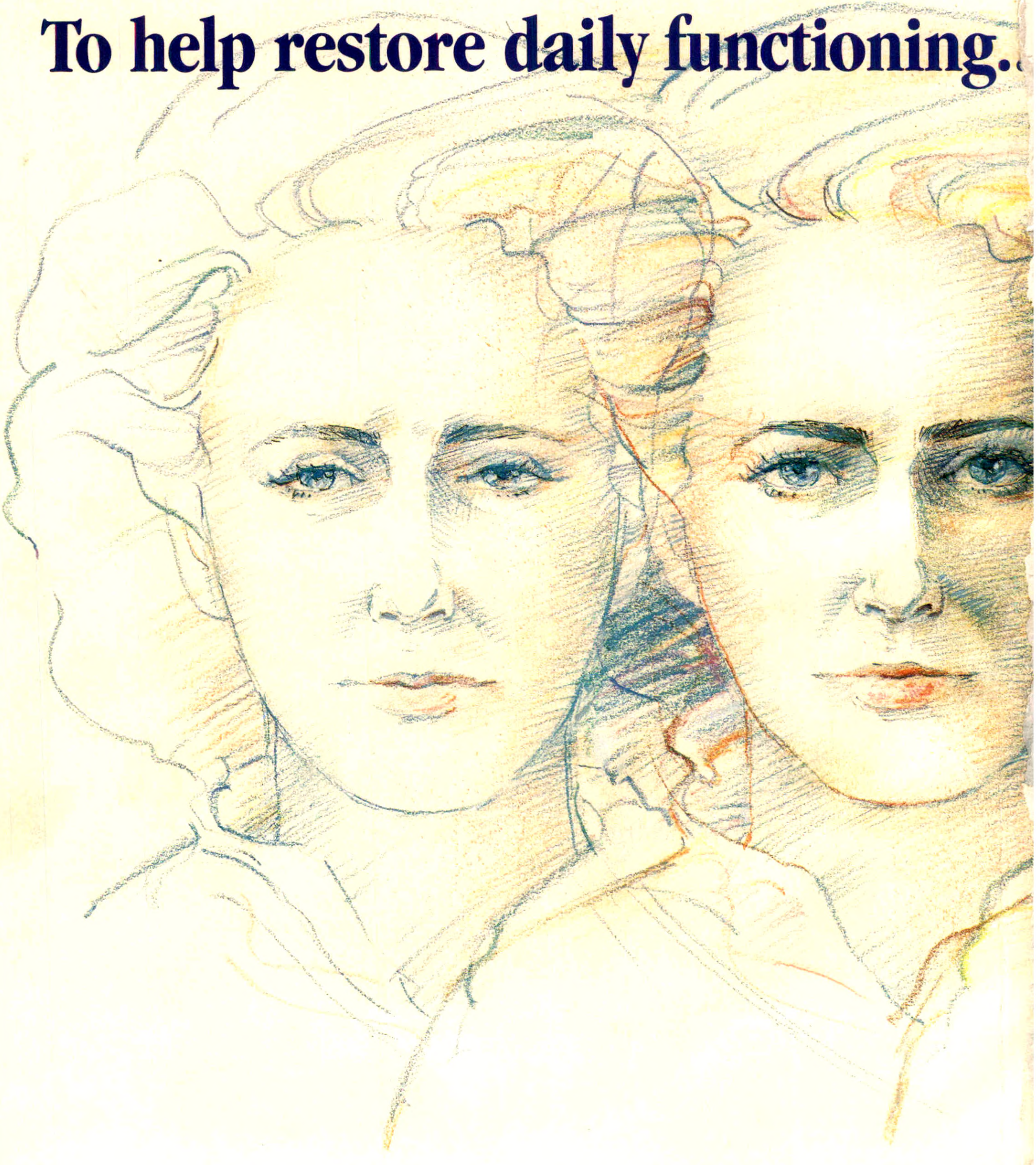

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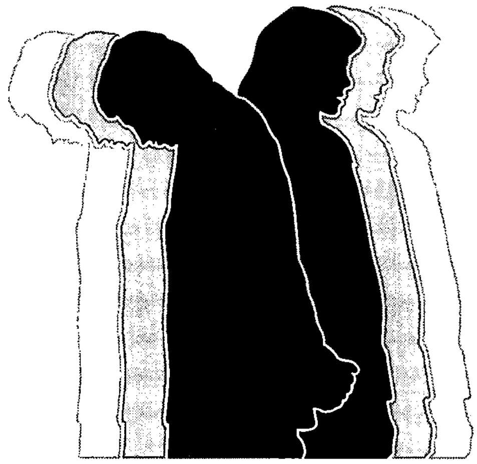

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### Approaches to Depression Management

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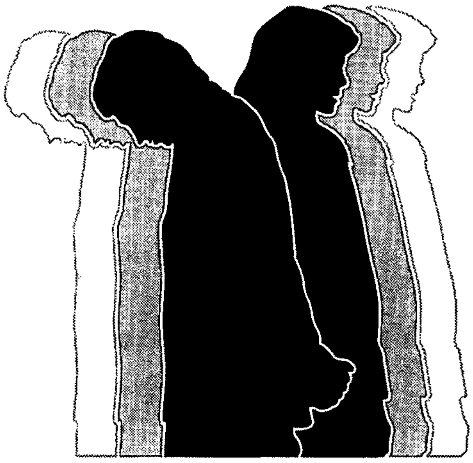

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THE AMERICAN JOURNAL OF PSYCHIATRY

*Editorial*

# New Year's Greetings

We recently had occasion to inspect an early edition of Dr. Johnson's famous *Dictionary,* and, our eyes falling on the entry for "Editor," read it as "He that reviles any work for publication." A second, more careful look at once revealed our perceptual error: We had mistaken one of those archaic eighteenth-century lower-case "s's" for an "l" and had fallen victim to a striking example of editorial "projective counteridentification." Although there is often much truth in unconscious mechanisms, editors are perhaps not always so arbitrary in their decisions as suffering authors perceive them; their biases are strictly controlled if not totally dispelled by the concerted advice of the multitude of informed colleagues whom they consult as expert reviewers. We (and our authors) must, therefore, proclaim our heartfelt appreciation to the following large community of scholars who have kept us on the strait and narrow path of editorial objectivity during the period from October 1, 1990, to October 31, 1991:

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**Deceased.

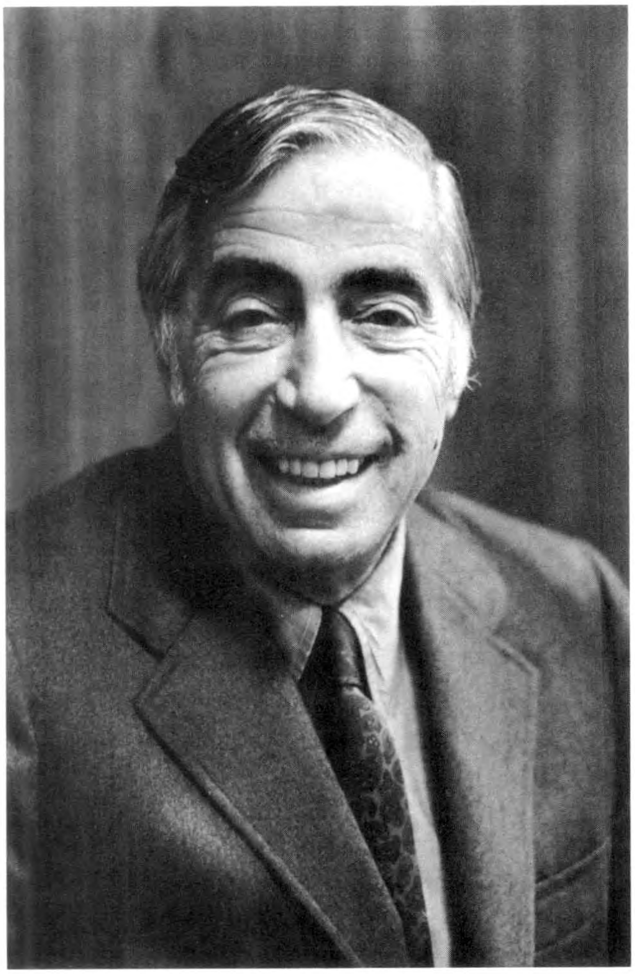
1991 has been a year of consolidation and progress for the *Journal.* Ms. Sandra Patterson, who assumed the Managing Editorship as 1990 ended, has firmly grasped the editorial helm, and with the unflagging help of her Assistant Managing Editor, Ms. Linda Loy, and her entire editorial staff, has introduced modern techniques of electronic publishing that have already made the production of the *Journal* more efficient and economical while markedly increasing our editorial control over the quality and accuracy of its pages. We must also express our deep gratitude for the help and companionship of our Deputy Editor, Dr. Nancy C. Andreasen, our Statistical Editors, Drs. John J. Bartko and Lee Gurel, and our thirteen Associate Editors; quietly, consistently, and selflessly given, their contributions are ever invaluable. Our sadness at losing Drs. T. Byram Karasu and Judith L. Rapoport, whose terms as Associate Editor expired at the end of the 1991 Annual Meeting, has been tempered by welcoming Drs. Gabrielle A. Carlson and David Spiegel to the Editorial Board. *Ave atque vale!*

During a year when our Association, like the world at large, has been plagued by fiscal problems, we are particularly grateful for the strong support and guidance of the Medical Director, Dr. Melvin Sabshin, and his staff, and to the Board of Trustees for their perception and understanding of the *Journal*'s needs. For their help in many matters large and small we must also express our appreciation to Drs. Robert J. Campbell III, John Hamilton, William A. More, Harold A. Pincus, Carolyn B. Robinowitz, Jeanne Spurlock, John A. Talbott, and Jack W. White; to Mses. Laura Abedi, Teddye Clayton, Carol Davis, Elizabeth Flynn, Nancy Frey, Debbie Goldberg, Alison Jones, Joan Lefkowitz, Karen Loper, Beth Prester, Arlis Richardson, and Jacqueline Young; and to Messrs. William E. Baxter, John Blamphin, George Campbell, Herbert M. Gant, Joel Klein, Ronald McMillen, Raymond J. Purkis, Jr., and Michael Roy.

As 1991 disappears astern, lashed to our masthead we wish all our colleagues and readers a safe and happy passage through whatever tempests of *glasnost* and *perestroika* still blow ahead.

J.C.N.

# In Memoriam



## John Paul Spiegel, M.D.
## 1911–1991

John P. Spiegel, the 103rd President of the American Psychiatric Association, died on July 17, 1991, at his home in Cambridge, Mass.

Dr. Spiegel was born in Chicago on March 17, 1911. He was a member of a well-known family that was prominent in community affairs and the business world. He graduated from Dartmouth College in 1934 and then entered Northwestern University Medical School, graduating in 1938. From 1938 to 1940 he had an internship at Michael Reese Hospital and a residency at that institution from 1940 to 1942. In 1942 he became a psychiatric consultant to the 12th Army Air Force in the Mediterranean Theatre of Operations. From 1944 to 1946 he was Chief of Professional Services of the Army Air Force Convalescent Hospital in St. Petersburg, Fla., and Chief of Psychiatric Services at Fort George Wright in Spokane, Wash.

Upon his completion of military service he returned to Michael Reese Hospital, where he was Chief of the Psychiatric Clinic from 1946 to 1951. He graduated from the Chicago Institute for Psychoanalysis in 1949 and was certified by the American Board of Psychiatry and Neurology in the same year. He also was an Associate Attending Physician at the Cook County Psychopathic Hospital in Chicago from 1947 to 1949. Dr. Spiegel was on the faculty of the University of Chicago School of Social Service Administration from 1949 to 1951. From 1951 to 1954 he was the Associate Director of the Institute for Psychiatric and Psychosomatic Research and Training at the Michael Reese Hospital. In 1953 he joined the faculty of the Department of Social Relations of Harvard University. He progressed there from Lecturer to Associate Clinical Professor of Psychiatry until 1966, when he became the Director of the Lemberg Center for the Study of Violence and Professor of Social Psychiatry of the Florence Heller Graduate School for Advanced Studies in Social Welfare at Brandeis University in Waltham, Mass. From 1973 to 1976 Dr. Spiegel was involved with the Family Transactions Project at Brandeis University, and from 1977 to 1980 he was the Director and Principal Investigator of the NIMH-funded Training Program in Ethnicity and Mental Health at the Heller School. In 1983 he became Adjunct Professor of Cultural Psychiatry at the University of Massachusetts Medical Center in Worcester.

Dr. Spiegel's outstanding career has been detailed because it illustrates the versatility and direction of his professional trajectory. He intimately worked with outstanding colleagues at Michael Reese Hospital—Roy Grinker, Sr., David Hamburg, Melvin Sabshin, Don Oken, and many other colleagues. These individuals have gone on to develop their own outstanding careers. Dr. Spiegel was farsighted in understanding, working in, teaching, and investigating areas of psychiatry that were at the time not the mainstream of our specialty. However, his pioneering path-making and leadership roles in various organizations have yielded very positive results as seen in the directions psychiatry is taking today—e.g., academic commitment, interdisciplinary research, and social and cultural psychiatry.

Dr. Spiegel was President of our Association from 1974 to 1975. He served with distinction on the Committee on Civil Defense (1955–1958); chaired the Task Force on Aggression and Violence (1969–1972); was a member of the Task Force on Third-Party Intervention in Community Conflict (1973–1974), the Committee on Interprofessional Services (1974–1978), the Commission on Standards and Practices of Third-Party Payments (1974–1977), and the Council on National Affairs (1977–1982); and was chairperson of the Task Force on Ethics and Cultural Issues in Psychiatry (1978–1980).

In addition, he was President of the American Academy of Psychoanalysis (1982–1983); the organizer and founder of the American Family Therapy Association; a member of the American Physicians Fellowship for the Israel Medical Association, the Sections on Medical Sociology and Family Sociology of the American Sociological Society, and the Board of Directors of the Foundations' Fund for Research in Psychiatry (1960–1965); and President of the Mental Health Film Board (since 1978), as well as a member of many other outstanding groups with whom he was actively involved.

His voluminous writings include such outstanding contributions as *Men Under Stress,* written with Roy R. Grinker, Sr., and many papers and books in other areas of our discipline. His published contributions covered such areas as acute stress, the family, emotional reactions to catastrophe, panic, systems theory, conflict resolution, cultural variations in attitudes toward death and disease, communications theory, psychoanalysis and psychotherapy, violence, terrorism, riots, peer review, generational conflicts, videotape techniques in psychiatric training and treatment, and the cultural aspects of the case of Anna 0. He published over a hundred papers and several books, some of which are now classics.

John Spiegel was a psychiatrist who was on the horizon of many now accepted areas of our field, when the dawn was just breaking. He was very interested in Pacific Rim and South Pacific cultures and was a founder of the Pacific Rim College of Psychiatrists.

In addition to all of his outstanding work on behalf of humane endeavors, he was married to Babette Shiller, an author and advocate of prison education. She died in 1975. Dr. Spiegel also had three daughters, a son, and eight grandchildren. Dr. Spiegel's pertinent contributions are very useful to us today as we confront many issues he insightfully addressed in his writings and presentations. It is with great appreciation that his colleagues and friends will know more of what he did for our Association, for psychiatry, and for our culture and society when they can view his work in a past life course perspective. He will be missed.

GEORGE H. POLLOCK, M.D., PH.D.

# The Meaning of Expressed Emotion: Theoretical Issues Raised by Cross-Cultural Research

Janis H. Jenkins, Ph.D., and Marvin Karno, M.D.

*The finding that expressed emotion is associated with the course of psychiatric disorder has generated a great deal of clinical and research interest in expressed emotion as an important risk factor. Theoretical elucidation of the construct of expressed emotion has lagged considerably behind this interest, however. The authors contribute to a dialogue on what is inside the "black box" called expressed emotion. They argue that cross-cultural research can provide an empirical basis for the theoretical grounding of expressed emotion factors. A comparative approach reveals that the construct of expressed emotion is essentially cultural in nature. The constellation of emotions, attitudes, and behaviors that are indexed by the expressed emotion method represent cross-culturally variable features of family response to an ill relative. Questions surrounding the cultural validity of the construct of expressed emotion, the qualitative dimensions of expressed emotion, and statistically significant cross-cultural variations in expressed emotion profiles are discussed. Finally, the authors provide an outline of diverse (cultural, psychobiological, social-ecological) features of expressed emotion. Anthropological analysis of expressed emotion reveals that although expressed emotion indexes a Pandora's box of diverse features, culture provides the context of variation through which these factors are most productively analyzed.*

(Am J Psychiatry 1992; 149:9–21)

Expressed emotion is currently among the most thoroughly investigated psychosocial research constructs in psychiatry (1–4). Developed some three decades ago by George Brown and his colleagues in England, the term "expressed emotion" refers to a global index of particular emotions, attitudes, and behaviors expressed by relatives about a family member diagnosed with schizophrenia. The specific factors that make up the construct of expressed emotion are criticism, hostility, and emotional overinvolvement. Several naturalistic studies have demonstrated the association of these factors with clinical relapse (5–8). Patients living in home environments characterized by high levels of expressed emotion are significantly more likely to experience a clinical relapse than are patients residing in households with low levels of expressed emotion. This finding has not surprisingly resulted in a great deal of clinical interest in a construct originally developed for purposes of basic research (9–12).

Theoretical elucidation of this research construct has lagged considerably behind clinical interest in expressed emotion. As Koenigsberg and Handley (13) observed in 1986, the elusive theoretical and empirical bases of the construct have gone unexamined. Precisely what is inside the "black box" called expressed emotion has

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somehow remained mysterious, as has been widely acknowledged (14, 15). In 1989 Vaughn (15), one of the principals of expressed emotion research, highlighted the fact that "substantial questions remain about the nature and meaning of the global expressed emotion index" (p. 2). This theoretical impoverishment provides a formidable research dilemma: ***the problem of prediction without understanding*** (16). The purpose of this paper is to provide a theoretical elucidation of the construct of expressed emotion, originating at the interface between anthropology and psychiatry. In our view, this analytic perspective is particularly suited to the task, since it is primarily in a cross-cultural, comparative light that the critical questions appear concerning the theoretical status of expressed emotion. Why have such striking differences in expressed emotion been observed across diverse populations and what can these differences tell us about the nature of the construct? What features, if any, do the specific components of expressed emotion have in common?

Any adequate theoretical elucidation must take into account the essentially cultural basis of the construct of expressed emotion. Culture can be defined as a generalized, coherent context of shared symbols and meanings that individuals dynamically create and recreate for themselves in the process of social interaction. In everyday life, culture is something people come to take for granted—their way of feeling, thinking, and being in the world—the unself-conscious medium of experience, interpretation, and action. Culture is thus the most generalized baseline from which individuals may deviate, an invaluable baseline for comparative studies of psychopathology. Specific attitudes and behaviors—recorded in the form of criticism, hostility, and emotional overinvolvement—are cultural dimensions of family response to and interpretation of what is professionally diagnosed as schizophrenic illness (4). In other words, what counts as criticism, hostility, and emotional overinvolvement is a matter of cultural definition.

Psychological anthropologists have shown that emotion can no longer properly be considered a private, intrapsychic, or psychobiological phenomenon. Instead, emotions—no less than other attitudes, beliefs, and behaviors—are substantially mediated by culture (17–20). To be specific, a culture provides its members with an available repertoire of affective and behavioral responses to the human condition, including illness. In addition, it offers models of how people should or might feel and act in response to the serious illness of a loved one. This may involve anger and hostility in one context or sadness and sympathy in another. The expressed emotion index is properly regarded as measuring cultural features because it taps a set of shared meanings and patterns of affective response to the problem of living with schizophrenic illness in a family setting.

Most important is consideration of critical comments, since this component accounts for the vast majority of what is really being measured by the construct of expressed emotion. Hostility and emotional overinvolvement are lesser variables of the expressed emotion triad and have been empirically observed far less frequently. Criticism within Anglo-American family settings, for example, may focus on allegations of faulty personality traits (e.g., laziness) or psychotic symptom behaviors (e.g., strange ideas). However, in other societies, such as those of Latin America, the same behaviors may not be met with criticism (21). Among Mexican-descent families, for example, criticism tends to focus on disrespectful or disruptive behaviors that affect the family but not on psychotic symptom behaviors and individual personality characteristics. Thus, culture plays a role in creating the content or targets of criticism. Perhaps most importantly, culture is influential in determining *whether* criticism is a prominent part of the familial emotional atmosphere.

The cross-cultural validity of the factors of expressed emotion necessarily requires close attention to indigenous definitions and expressions of criticism, hostility, and emotional overinvolvement (4). Are these affective domains observable in social interaction? Are they communicated in generally recognizable ways through language, paralanguage, and actions? Based on data generally available in ethnographic accounts, our own view is that verbal criticism within families is likely to occur in most of the world's cultures. For example, criticism has been noted in such geographically diverse groups as the Pintupi aborigines of Australia (22) and the Inuit Eskimos (23). Nevertheless, we would also expect a great deal of cross-cultural variation in the frequency, intensity, nature, and meaning of criticism within families. In the light of variations in social structure, household organization, and cultural constructions of the self, we might expect emotional overinvolvement to be less common across cultures. However, there appear to be some types of behavior reflecting emotional overinvolvement among the Inuit Eskimos (24), for example. Certainly the basic features of emotional overinvolvement are commonly encountered in clinical practice in Europe, Latin America, Australia, and North America. The cross-cultural applications and likely limitations of the construct of emotional overinvolvement are matters for empirical demonstration.

In the absence of such empirical testing, it would be a mistake to conclude that expressed emotion factors are a priori culture-bound to British or Anglo-American families. The family factors themselves are neither culture-bound nor ethnocentric; it is the cultural validity of their application that must concern us. Evidence for expressed emotion factors has definitively been found —in culturally specific ways—in British, Mexican-descent, and Anglo-American contexts. Further studies of the frequency and distribution of the basic elements of the expressed emotion index—as well as an interpretation of their nature and meaning—are suitably the subject of inquiry. In the absence of adequate data on this subject, it remains to be seen whether societies exist in which a complete absence of these factors can be documented. Given the common context of families living with the difficulties generated by schizophrenic illness, it is reasonable to expect some cross-cultural similarities in the kinds of things relatives might find objectionable and therefore deserving criticism. Given variations in cultural definitions of behavior and emotion, however, it is also reasonable to expect substantial differences in the things family members feel they can appropriately tolerate. Thus, the research domain of criticism clearly requires a cross-cultural perspective.

## THE CULTURAL AND CLINICAL EXPORT OF EXPRESSED EMOTION

In the last 10 years alone, well over 100 English-language journal articles on expressed emotion have appeared. Popular topics include the role of expressed emotion in the course of schizophrenia (5–8), family treatment (9, 25), correlative or "streamlined" measures of expressed emotion (26–29), and vigorous protests by relatives in the United States who perceive researchers as indicting them for causing or maintaining their family member's illness (30). As an outcome measure associated with the clinical course of illness, expressed emotion has been applied across a variety of cultural and clinical groups. Indeed, the study of expressed emotion has become an international preoccupation traversing five continents. Research is complete or underway in Europe (England [4, 5, 31, 32], Denmark [33], Italy [34], France [35], Spain [unpublished paper by E. Gutierrez], and Germany [36]), North America (among Anglo-Americans [7], those of Mexican descent [8], and African-Americans [37]), Asia (Taiwan [38]), India (33, 39, 40), North Africa (Egypt [personal communication from A. Wilson]), and Australia (41). Moreover, although this work was initially restricted to schizophrenic populations, the study of expressed emotion has assumed new applications in research for both psychiatric and nonpsychiatric conditions. Studies have been conducted on affective disorders such as depression (42) and bipolar illness (43), dementia (44), anorexia nervosa (45), asthma (46), stroke (47), obesity (48), and intractable childhood epilepsy, autism, Parkinson's disease, and inflammatory bowel disease (15). To summarize, studies of expressed emotion have been applied to a variety of both cultural and clinical populations.

It is not our purpose here to review the status of the now numerous expressed emotion replication studies; summaries and critical reviews of these findings are available elsewhere (13, 49). We simply note here that although many investigators found support for the association between expressed emotion and outcome (41), others failed to confirm this relationship. For example, one controlled intervention trial that focused on medication-compliant patients found no association between expressed emotion or controlled dosage and clinical outcome (50). That some of these findings might constitute an empirical challenge to the confirmatory studies is compromised by these investigators' use of divergent, or even flawed, methodological procedures (32–36; unpublished manuscript of E. Gutierrez). For example, Mintz et al. (51) reported that the negative results of a study by MacMillan et al. (32) do not constitute a legitimate challenge to the relationship of expressed emotion to clinical relapse because the statistical analyses used by MacMillan et al. were inappropriate.

As summarized by Vaughn (15), the North American replications of the earlier British studies by Brown and his colleagues were "distinguished by their comparable approaches to diagnosis, expressed emotion assessment, and the definition of relapse as the return or exacerbation of specifically schizophrenic symptoms" (p. 15). Since these studies retained methodological consistency of approach across these different populations, they constitute a first step toward consideration of the cross-cultural relevance of expressed emotion. We proceed on the assumption that the relevance of expressed emotion to the course of illness has satisfactorily been demonstrated and that the relationship between expressed emotion and relapse has been replicated more often than not (52). Therefore, although individual variability and complexity in the salience of the association between expressed emotion and outcome exist, expressed emotion is appropriately regarded as a major risk factor in the course of a psychiatric illness (15, 49, 53).

## THE THEORETICAL STATUS OF THE CONSTRUCT OF EXPRESSED EMOTION

It might seem reasonable to assume that the proliferation of expressed emotion research is based on the empirical testing of an articulated set of assumptions concerning the theoretical status and parameters of the construct. Unfortunately, this does not reflect the current situation. We need to know what expressed emotion is measuring or tapping. In the absence of such an understanding, expressed emotion research endeavors are at risk of becoming repetitive and mindless exercises without meaning.

Several factors seem to have contributed to this state of affairs. First, the refined and systematic measurement techniques have focused on specific components of expressed emotion (criticism, hostility, and emotional overinvolvement). This focus is reasonable in the wake of research results implicating expressed emotion in relapse (5–8). The very specificity of this empirically derived global construct seems to have diverted scientific interest in a broader understanding of the nature of expressed emotion.

Second, expressed emotion summarizes a seemingly disparate constellation of family affects, attitudes, and behaviors. It is not immediately obvious just how or why these factors cohere or should be examined together. In fact, these features of family interaction do not necessarily go together conceptually. The perhaps infelicitous coding and labeling of what has come to be known as expressed emotion have happened by empirical accident.

Third, because of the microanalytic rating technique and highly specific empirical focus of expressed emotion research, attention has been diverted from questions concerning the validity of what is being measured. This shortcoming is by no means unique to expressed emotion research but is true of empirical psychiatric research endeavors more generally. As part of a paradigmatic definition of the pertinent research questions and methods for their investigation, psychiatric research efforts today typically do not prominently concern questions of validity, interpretation, or meaning (54). In the case of expressed emotion research, this presents a problem because explication of expressed emotion, as an empirical index of relatives' subjective experience and response, requires a theoretical bridge from behavior to meaning.

The theoretical issue that has garnered the most attention—the question of how expressed emotion might influence the clinical course of illness—remains largely unelaborated. The working assumption, largely unchanged over the past two decades, is that emotional arousal constitutes a major stressor for persons with schizophrenic illness. Overarousal through exposure to high degrees of negative affects, the theory asserts, may result in relapse or exacerbation of florid symptoms (5, 6). In 1987, Kuipers (2) summarized the physiological evidence for this assertion as inconclusive. An understanding of the physiological aspects of expressed emotion requires further research (17, 49) but is not our principal concern here. Our interest lies instead with the cultural and psychosocial status of the construct of expressed emotion on the grounds that it is insufficient merely to link expressed emotion with relapse.

## CLUES TO THE NATURE OF EXPRESSED EMOTION

According to Brown (3), the search for the family factors that ultimately came to be known as the expressed emotion construct originated with an interest in the everyday features of family life. He reported that he and his colleagues assumed that anything of importance was to be found in nonpathological communications rather than in presumed pathological family features. This emphasis on the ordinary was conceptualized as a shift away from psychiatric assumptions, current in the 1950s, that psychopathological family features held etiological significance for schizophrenia.

Despite the shift in emphasis from etiology to course of illness, the British focus on family factors was deeply influenced by the long research tradition in North American psychiatry of studying schizophrenia in relation to family factors and communication. The underlying premise of expressed emotion research—that emotion is an atmosphere that permeates interactive settings—was pioneered by Harry Stack Sullivan (55). The empirical investigation of particular family affects by the British researchers represented further developments of the research traditions initiated by Bateson et al. (56), Wynne et al. (57), and Lidz and Fleck (58). Even so, there are no directly equivalent concepts in the family psychopathology literature for the specific features that make up the construct of expressed emotion. Criticism, a prosaic feature of family communication, is by no means restricted to families of individuals with schizophrenia, and criticism is of a different order than etiological notions such as double-bind, pseudo-mutuality, and schism. The factor of emotional overinvolvement would appear most closely to approximate dimensions of intrusiveness as investigated by Lidz and Fleck (58). Their studies of family relations claimed an inordinate intrusiveness of parents toward their disturbed offspring. In contrast to these researchers' claim that such features typified disturbed families, the emotional overinvolvement factor has not been empirically observed with great frequency in families of individuals with schizophrenia.

Although the etiological framework of these studies was appropriately discarded for lack of empirical evidence, these early family studies served to identify the kind of material out of which the specific expressed emotion factors were formed. Conceived by Brown and his colleagues as variables that might prove important to the course of an established schizophrenic illness, particular family affects that could potentially influence an often sensitive and fragile process of adaptation to the social world were sought. A strength of the expressed emotion research tradition is its contribution toward the reliable operationalization of such factors with greater precision than had previously been established (59; unpublished 1978 manuscript of G. Brown et al.).

Differences between high and low expressed emotion profiles provide clues to the nature of expressed emotion. In general, explanations of such differences have not progressed beyond the basic hypothesis of Brown et al. some two decades ago (5). This general formulation holds that varying levels of expressed emotion are linked to relatives' own personality traits, to degrees of patient psychopathology, or to a combination of these factors. Hooley (14) argued that differences in expressed emotion are linked to the tendency of relatives to attribute blame to either the patient or the illness and that these attributions can serve as indexes of relatives' personality characteristics. The contribution of differing levels of patient psychopathology has been examined through analyses of the relationship between expressed emotion and the severity of patients' symptoms. Levels and types of patient morbidity have been investigated by severity of symptom scores and behavioral disturbances (symptoms of irritability, destructiveness, suicidality, and bizarre behavior) (6). Results of these analyses have shown expressed emotion to be independent of measures of patient psychopathology and behavioral disturbance (5–8). Expressed emotion as a behavioral manifestation of actual ongoing family interaction has also been confirmed (49, 60).

A refined qualitative analysis of differences in expressed emotion profiles has been provided by Vaughn (61). She systematically identified four factors that differentiate relatives with low versus high expressed emotion: 1) respect for patients' relationship needs, 2) attitudes toward the legitimacy of the illness, 3) level of expectations for patients' functioning, and 4) emotional reactions to the patient's illness. For instance, a British relative is rated low in expressed emotion if he or she displays respect for the patient's need for interpersonal distance, considers the illness to be outside of the patient's control, maintains few expectations for normal functioning, and manifests a concerned but "cool," "easygoing," or "flexible" response to the problem (62, pp. 117–118). The four domains identified by Vaughn are useful in accounting for observed variations in family response and provide an important step in the development of a broader conceptual model of expressed emotion. However, Leff and Vaughn (62), citing their experience in studies in London and Southern California, claimed that "these differences hold across cultures and across diagnostic groups" (p. 112). This sweeping generalization cannot be sustained on the basis of only two English-speaking cultures.

Although the qualitative factors identified by Vaughn provide valuable guidelines for analysis of intracultural variability in expressed emotion, there are several ways in which we can anticipate that culturally distinct features will also come into play. For example, that such dispassionate traits as remaining "cool" or "easygoing" are highly valued in British culture is well-known; it is nonetheless evident from an anthropological point of view that this culturally specific interpretation of low expressed emotion cannot be expected to apply cross-culturally (4).

Greenley (63) has developed an additional scheme for conceptualizing expressed emotion. He proposed broad parameters for expressed emotion as high-intensity interpersonal social control. In Greenley's formulation, the dominant affects of anxiety and fear on the part of relatives lead them to attempt to control the patient socially through criticism and overinvolvement. Relatives who identify the problem as one of mental illness are hypothesized to have a reduced fear/anxiety reaction and therefore a lesser need for high-intensity interpersonal social control (i.e., expressed emotion). This basically social conceptualization provides us with an interesting but partial explanation. The complex of connections between motivation and action in the form of social control necessarily entails a broad array of cultural, psychological, and contextual levels of explanation. As Greenley's analysis illustrates, anxiety and fear may not be the dominant sentiments that motivate particular relatives. We can suggest many more, such as anger, sadness, despair, shame, and guilt, that may be prominent. Indeed, motivating affects can be expected to vary cross-culturally.

Moreover, sizable numbers of Mexican-descent and Anglo-American relatives feel a range of dysphoric affects—including anxiety and fear—despite their belief that their relative is afflicted with a mental illness. For example, Anglo-American relatives may see the problem as one of schizophrenia or negatively valued personality traits (e.g., laziness). Either of these may be regarded as the sole problem or both may be considered in tandem. These relatives may concede that disease may well be present, but they might also feel that certain negative personality traits are present as well (64). The cultural perception that undesirable personality traits are involved is related to core American values such as responsibility, autonomy, independence, and initiative (21). This suggests a more complicated and contradictory chain of cultural logic for interpreting and responding to the illness.

## CROSS-CULTURAL APPROACHES IN EXPRESSED EMOTION RESEARCH

To illustrate the cross-cultural variability of expressed emotion, we examined the results of published studies using comparable methodological techniques. The studies compared are the British studies by Brown et al. (5) and Vaughn and Leff (6), the study of Anglo-Americans in Southern California by Vaughn et al. (7), our group's study of Spanish-speaking subjects of Mexican descent (8, 21), and the study of Hindi-speaking Indians by Wig et al. (33, 39, 40). The latter study was part of the 12-country international World Health Organization (WHO) study of determinants of outcome in schizophrenia. Only two settings in the WHO study were chosen as sites for concurrent expressed emotion studies: Aarhus, Denmark, and Chandigarh, North India. As reported by R. Day (unpublished 1982 paper), logistic and methodological difficulties in carrying out the Danish study apparently render the data problematic for comparative purposes. In this section, we focus on the Indian and Mexican-descent studies because these provide a greater cross-cultural contrast than the English-speaking British and Anglo-American samples.

The following summary points (which apply to the British and Anglo-American studies as well) can be made concerning the Mexican-descent and Indian studies. First, both the Mexican-descent and Indian outcome studies suggest the importance of the family emotional milieu in the course of schizophrenia. Second, analyses of these cross-cultural data establish significant differences in levels of family display of criticism with respect to schizophrenic illness. Third, these data shed light on previous results concerning observed sociocultural variation in schizophrenic outcome, as documented by the WHO International Pilot Study of Schizophrenia (IPSS) (65).

### *Mexican-Descent Study: Expressed Emotion in Southern California*

Although the study of expressed emotion among Anglo-Americans in Southern California (7) constitutes an important replication of the earlier British studies, we believe that the issue of cross-cultural replication could be better addressed through the more culturally and linguistically distinct contrast provided by families of Mexican descent in Southern California (8, 21, 64, 66).

The goals of our study were 1) to examine the cross-cultural validity of expressed emotion among families of Mexican descent, 2) to conduct a replication study of the relation of expressed emotion to schizophrenic outcome, and 3) to examine expressed emotion in relation to family conceptions of the nature and etiology of schizophrenic illness (e.g., *nervios* caused by improper blood circulation) (66). The majority of the immigrant families studied were relatively unacculturated monolingual Spanish-speakers of lower socioeconomic status who identified themselves as *Mexicanos.* The study of expressed emotion among these subjects holds special relevance because the family is typically described as central to the Mexican and Mexican-American sense of self, identity, and well-being (67, 68).

Procedures for the recruitment of patients, the principal methods, sample characteristics, outcome findings, and Spanish-language adaptation of the Camberwell Family Interview have been summarized elsewhere (8). The cross-cultural use of expressed emotion rating scales requires adaptation of the underlying principles of the expressed emotion index and is essential to a culturally meaningful study. To enhance the validity of these scales in the Mexican-descent study, a pilot project was conducted to adapt them in the light of these families' particular cultural context.

The operational definition of criticism was "verbal behavior that is observed through tone of voice or content of speech which clearly conveys dislike, resentment, or disapproval." In the Spanish language, both content and vocal characteristics of speech may communicate criticism, and this approach was therefore deemed linguistically appropriate. The rating criteria for the expressed emotion scales, case studies, and the adaptation of the scales for the Mexican-descent study have been more fully summarized elsewhere (4; unpublished 1978 manuscript of G. Brown et al.).

Although we found that the scale for criticism could be applied with relative facility, the scale for emotional overinvolvement required more adaptation. The basic attitudinal, behavioral, and affective domains measured by the emotional overinvolvement scale were retained for rating purposes, but the content of each of these domains was redefined in the light of the values and norms of the Mexican-descent subjects. It was ethnographically determined that cultural guidelines for kin involvement with an ill relative could be identified and that the families themselves recognized instances when cultural boundaries were surpassed. Indigenous recognition of particular attitudes and behaviors as unusual is crucial to the cross-cultural validity of the concept. For example, among the minority of Mexican-descent relatives with high scores on the emotional overinvolvement scale, several relevant features emerged. These included reports of suffering in relation to *nervios* (an indigenously defined category for distress) and cessation of a family orientation in favor of a relatively exclusive dyadic relationship with the patient. For example, a Mexican mother who stops interacting with all other family members and has suicidal wishes and an extreme problem of *nervios* in relation to the schizophrenic illness of her child is behaving in a culturally unusual manner. (Only 11 [11%] of 109 Mexican-descent relatives were rated high on emotional involvement.) Other family members of the relative with a high emotional overinvolvement score would sometimes describe that person as having "lost it" or going "too far." Also important is the fact that such behaviors were not considered culturally praiseworthy. The matter of cultural definition is crucial to the problem of validity. Behavior reflecting high levels of emotional overinvolvement are culturally unusual, even in the face of serious or long-term family illness.

As found in the British and Anglo-American studies, expressed emotion was significantly associated with the course of schizophrenic illness for patients who experienced some degree of symptomatic recovery following hospitalization for an acute psychotic episode. The study also found a significantly lower rate of high levels of expressed emotion among Mexican-descent relatives than among their Anglo-American counterparts. Our group reported that "this documentation of variations in expressed emotion profiles across distinctive cultural contexts provides support for the IPSS WHO hypothesis that intrafamilial behaviors may account for different prognoses for schizophrenic outcome in different cultural settings" (8, p. 151).

### *Indian Expressed Emotion: The Chandigarh Study*

Like the Mexican-descent study, the Chandigarh study was concerned with the transfer of the expressed emotion rating scales to culturally distinct settings and with the observation of variations in the outcome of schizophrenic patients (33, 39, 40). The Chandigarh study found that relatively few (23%) of the Indian households were classed as high in expressed emotion and that none of the relatives had scores on the emotional overinvolvement factor that were considered high in previous studies (33). Also unlike previous studies, the only expressed emotion factor found to be significantly related to outcome of schizophrenic patients was hostility. These results suggest substantial cross-cultural differences not only in the degrees and types of expressed emotion observed for the Chandigarh subjects but also in the particular factor or factors that may mediate outcome in schizophrenia.

Wig et al. have considered methodological factors that bear on their results. These primarily concern issues of interrater reliability. The assessment of the reliability of hostility—the only predictive expressed emotion factor in their study—was difficult to obtain because it was observed so infrequently. Wig et al. (39) reported that because of this they could not be certain about the transferability of ratings of hostility. However, they concluded that "the findings suggest that this assessment is also likely to be transferable across the linguistic frontiers without significant distortion" (p. 158). For emotional overinvolvement, they reported that one rater's tendency to underrate on this scale led to ambiguities. This difficulty, they asserted, was due to technical training problems rather than the cultural validity and adaptation of these scales as used in the Indian context.

In the light of the need to culturally adapt the rating scales for use in the Mexican-descent study (24), it seems that cultural issues would necessarily be of relevance to an adequate understanding of emotional overinvolvement scores for Indian relatives. The cultural validity of the protocol and rating scales must be established for a meaningful cross-cultural extension of these ratings. Although Wig et al. discussed problems of reliability, the cultural validity of the expressed emotion ratings should also be elaborated. Cultural issues—in terms of normative baselines, rules for familial display of affect, and culturally specific meanings—certainly are important and require careful consideration in the rating process and transfer of the expressed emotion method to Indian culture. The finding that only hostility predicted outcome might signal the necessity of substantial cultural adaptation and interpretation of these scales in the Indian setting. With respect to the negative finding for higher levels of emotional overinvolvement, it may well be that these are virtually absent in the Indian context. It might also be, however, that the findings are related to methodological difficulties related to the cultural validity and adaptation of this scale in Hindi among the Chandigarh relatives. To the limited degree that emotional overinvolvement is present at all, it would undoubtedly be expressed differently in Hindu families than it is in British families.

Another cultural issue raised by the Chandigarh study is interpretation of the finding that expressed emotion profiles among the Chandigarh relatives were surprisingly low or absent and that only hostility was associated with clinical course of illness (40). The finding for hostility is unique. Although the profiles indicative of low expressed emotion in India may substantially account for the good prognosis observed for schizophrenia, it is possible that some other yet unidentified set of sociocultural factors might also account for these results. Another variable in interpreting these results is a clinical factor: unlike the subjects in the other expressed emotion studies, patients in Chandigarh were recruited at the time of their first contact with psychiatric services. Better prognosis is common for first-admission patients.

## EXPRESSED EMOTION PROFILES IN CROSS-CULTURAL CONTEXT

Comparison of expressed emotion profiles shows that Indian families scored lowest (23%), followed by the Mexican-descent (41%), British (48%), and Anglo-American (67%) households (5–8, 33). The Indian households were strikingly lower than all others, and our group reported statistically significant differences between Mexican-descent and Anglo-American families (Yates-corrected $\chi^2=7.92$, df=1, $p<0.01$) and between British and Anglo-American families (Yates-corrected $\chi^2=5.84$, df=1, $p<0.02$) (8). The impressive range and significant differences in these expressed emotion profiles make it evident that it is only in cross-cultural perspective that the critical questions come to light: Why are the Indian scores so low? What about the statistically nonsignificant differences between the British and Mexican-descent households? Is it reasonable to conclude, as certainly no British or Mexican-descent relative ever would, that there are no cultural differences in familial emotional climate of their households? How is it that Mexican-descent and Anglo-American families in the same geographic locale (Southern California) differ so significantly? Why do English-speaking Anglo-American households score significantly higher than their British counterparts?

In considering this latter question, Leff and Vaughn (62) commented only that the differences between London and Los Angeles relatives were "interesting, though not unexpected" (p. 184). Completely unelaborated is the pressing issue of how and why these striking differences might be interesting or expected. Curiously, cultural evidence and hypotheses that could account for differences in expressed emotion profiles are unexamined. Leff and Vaughn argued only that it is important to consider noncultural factors, such as number of hospital admissions and social class. They concluded that neither of these factors proved informative for the observed differences.

Another factor considered by Leff and Vaughn is the historical epoch of each of these studies. This is potentially relevant because the American work was conducted in the 1980s and the British research in the 1960s and 1970s. However, the authors did not define the concept of historical epoch, nor did they discuss how or why expressed emotion might have changed historically. Although in our view two decades is far too abbreviated a historical period for major cultural changes in socialization of affect to occur within family settings, this remains a relevant topic for investigation. Another domain, that of fluctuations in the political economy in the West, could also partially mediate attitudes toward deviance in general and mental disorder in particular (69).

A related factor of importance to an understanding of expressed emotion is social class. Drawing on data from the Mexican-descent study, our group conducted an analysis designed to determine the relative influence of ethnicity and social class variables on expressed emotion (21). We compared a matched Anglo-American subgroup incorporating all lower socioeconomic status families available in the study of Vaughn et al. (7) with the first 30 patients entered into the Mexican-descent study. Comparison of subgroups was necessary because the Anglo-American study group included a full range of social class levels but the Mexican-descent study group included only the lower socioeconomic levels. With social class held constant, an even more striking difference was observed between these two ethnic groups: 83% of the Anglo-American patients, compared with only 43% of their Mexican-descent counterparts, resided in households rated high in expressed emotion ($p<0.003$, Fisher's exact test). These results revealed that, in addition to a strong main effect for ethnicity, levels of expressed emotion are also independently related to socioeconomic status among Anglo-Americans.

The percentage of households with high levels of expressed emotion in the lower-status Anglo-American subgroup was higher than that in the entire Anglo-American study group of 69 families (83% versus 67%). Analysis of variance and covariance revealed that these differences in expressed emotion were not significantly related to patient characteristics (e.g., age, gender, number of hospitalizations, premorbid functioning), relatives' characteristics, or type of household (parental, marital, sibling). The results of the comparison of Anglo-American and Mexican-descent households matched in socioeconomic status provide strong evidence for major differences in cultural styles of emotional response to schizophrenic illness within the family (6). They also provide evidence for the importance of taking into account intracultural variations in expressed emotion, as evidenced through indexes of social class (21).

In addition to overall differences in expressed emotion profiles, the British, Anglo-American, and Mexican-descent studies also reported significant differences in the distribution and mean scores for criticism, hostility, and emotional overinvolvement. For criticism, a low mean score of 1.8 critical comments was obtained for the Indian sample, compared with 3.3 for the Mexican-descent relatives, 6.9 for the Anglo-American relatives, and 7.5 for the British relatives (8, 62). The cross-cultural differences in the mean scores and reported distributions for critical comments, which ranged from 0 to 61, suggest not only cultural variations in family tolerance of schizophrenic illness but also differences in the upper and lower thresholds of criticism observable within these familial environments (62).

Considerably less quantitative variability has been found on measures of emotional overinvolvement and hostility. Perhaps the most notable cross-cultural finding with respect to emotional overinvolvement is the relatively small number of relatives who were rated high on this factor. None of the Indian relatives, 11% of the Mexican-descent relatives, 15% of the Anglo-American relatives, and 21% of the British relatives had scores on this item that were considered high. These results are important because, as already noted, they do not provide cross-cultural support for the idea that families of patients with schizophrenia are appropriately characterized as disturbed or pathological in their interpersonal relations. Indeed, for the Indian relatives the entire concept of emotional overinvolvement appears to be of highly limited relevance. The Mexican-descent data, along with data from other investigations, provide evidence that counters clinical and ethnographic stereotypes in the literature characterizing Latin American women as overprotective and self-sacrificing (8, 70). Results for ratings of hostility reveal that only 16% of Indian, 18% of English, and 13% of Mexican-descent relatives were found to be hostile. The higher figure of 28% reported for Anglo-Americans parallels the relatively higher degree of criticism displayed by those family members (62).

These results demonstrate relatively minor quantitative differences in the levels of emotional overinvolvement and hostility but do not address possible differences in content and qualitative features of these factors. This important topic deserves close attention and has been addressed to some extent in the context of individual studies (4, 21, 61, 62). We turn our attention now to consideration of what sorts of qualitative features might be implicated and their meaning for the theoretical grounding of the construct of expressed emotion.

## AN ANTHROPOLOGICAL ANALYSIS OF THE EXPRESSED EMOTION CONSTRUCT: DIFFERENCES IN LEVELS OF *WHAT*?

In George Brown's excellent 1985 essay on the discovery of expressed emotion (3), he related that upon commencement of his second study of expressed emotion, he knew that something about family life was important to the course of illness but not what. Brown and his associates developed an array of measures of family factors that included not only criticism, hostility, and emotional overinvolvement but also warmth, positive remarks, dissatisfaction, tension, irritability, and (for marital situations) the quality of marital relations (unpublished 1978 manuscript of G. Brown et al.). Only subsequent empirical research served to specify which expressed emotion components were associated with clinical relapse. In discussing the differences between a causal model (that which relates measures in terms of causal links) and a theory (that which explicates what the measure represents), Brown (3) noted that "just *what* is involved cannot be known unless it is clear what the measure represents theoretically. It is inevitable that model and theory will not keep step, and progress in science can be said to come from the struggle to close the gap between them" (p. 21; emphasis added).

In our view, the unknown and theoretically overarching something or somethings indexed by the global construct of expressed emotion are culturally constituted features of kin response to an ill relative. Culture, as a system of shared meanings and symbols, offers the most powerful explanation for observed variations in expressed emotion in different populations. The culturally constituted features—attitudes, affects, and behavior on the part of family members toward their ill relative—are what is being indexed through measurement of expressed emotion. A theoretical accounting of what is inside the "black box" called expressed emotion must therefore prominently concern the concept of culture.

Other theoretical accounts are also necessary. Relatives' responses to a family member's illness include a complex of features that dynamically interact with one another. An abbreviated outline of some of these factors follows.

## FEATURES OF EXPRESSED EMOTION

1. *Cultural interpretations of the nature of the problem.* Relatives' interpretations of the problem are their views of its nature, cause, and course (e.g., laziness caused by illicit drug use that would improve if the patient exercised willpower). These interpretations mediate relatives' emotional responses to the problem (64, 66). The works of Edgerton (71) and Kleinman (72) serve as anthropological classics on this topic.

2. *Cultural meanings of kin relations.* Relatives' responses to an ill family member are formulated in the context of culturally prescribed definitions of family life that suggest appropriate patterns for interpersonal relations among kin. Family relations have sometimes been characterized on a continuum between an individualistic orientation and a family orientation (73).

3. *Identification of cultural rule violations.* Cultures define what counts as behavior deserving of legitimate criticism. Identification of cultural rule violations (e.g., failure to be independent) varies in relation to the values, norms, and expectations in particular settings and in accord with culturally defined statuses that may legitimately exempt individuals from criticism (74).

4. *Vocabularies of emotion.* Cultures differentially construct a universe of discourse on emotion, or ethos, within which the relatives' responses to illness are articulated. Emotions that are culturally salient (e.g., sadness as opposed to anger) provide models that may shape how individuals might or should feel in a given situation (22, 75).

5. *Relatives' personality traits or predispositions.* Although the subject has yet to be explored, variations in individual personality or temperament are common partial explanations for why relatives might display varying degrees of expressed emotion (49). Responses indicative of high levels of expressed emotion may also be partially explained by some degree of shared (and possibly genetic) vulnerability to pathology for relatives and patients alike (76). Variations in relatives' attributional styles have also been explored (14).

6. *Degrees and kinds of patients' psychopathology.* It is frequently hypothesized that variations in degrees of patients' psychopathology might account for differences in relatives' expressed emotion. This assumption undoubtedly holds merit in some instances (e.g., extremely bizarre schizophrenic behavior); however, empirical examination has repeatedly demonstrated a nonsignificant relationship between severity of patients' symptoms and relatives' expressed emotion (5–8).

7. *Family interaction dynamics.* Typical family patterns of identification, communication, and separation can also be expected to shape relatives' emotional responses to an ill family member. Displacement of hostility, ridicule, protection, and devotion, for example, may vary in accord with individual family dynamics. In addition, the socialization of particular family dynamics may be culturally mediated. In a study of schizophrenia in rural Ireland, Scheper-Hughes (77) found that the youngest sons were often expected to preserve the family's identity and longevity. Failure to do so typically generated critical and hostile reactions.

8. *Attempts to socially control a deviant relative.* Expressed emotion can be considered a behavioral intervention strategy of families that is designed to restrict the objectionable activities and actions of a deviant family member (63).

9. *Availability and quality of social supports.* The compositional features of households, including size and kin type, may influence a relative's expressed emotion. For example, expressed emotion may be higher among parents than spouses (8). In an Australian study (41), expressed emotion more successfully predicted relapse in single-parent households than in two-parent homes. Social supports, like life events, might mediate the impact of expressed emotion (62).

10. *Historical and political economic factors.* It has been suggested that explanations for differences in expressed emotion profiles may change over time (62). Changing social and economic conditions may influence the emotional climate of a society in general, with repercussions for how families reflect societal attitudes toward individuals identified as deviant (69). There is also evidence for differences in expressed emotion in relation to social class (21).

We will focus on the first four of these features because the emphasis of this paper is on the cultural basis of the construct of expressed emotion and because these factors have been neglected.

### *Cultural Interpretations of the Problem*

Cultural conceptions of mental disorder—indigenous notions of the nature, cause, and course of illness—have long been a focus of anthropological investigation (64, 66, 71, 72). To what extent do cultural conceptions of the illness mediate expressed emotion in families? Can such conceptions create a culturally legitimate status that inhibits high levels of criticism? Is the cultural locus of the problem deemed to be a personality problem, an illness entity, or an external malevolent agency? Several authors (14, 61) have identified this issue as important to the formation of expressed emotion attitudes. The identification of this factor as a specifically cultural issue in psychiatric research has been slow in coming, however.

In our study of the Mexican-descent relatives (64, 66), the concept of *nervios* served as a cultural label for schizophrenic illness. The term *nervios* is in broad cultural use for a wide range of everyday distress (e.g., tension) and severe illness conditions (e.g., schizophrenia, depression). This inclusive use of the term serves to destigmatize such conditions. Since severe cases of *nervios* are not considered blameworthy or under an individual's control, the person who suffers its effects is deserving of sympathy, support, and special treatment. Moreover, severe cases of *nervios* are potentially curable. It is interesting to note that Mexican-descent relatives do not adopt another possible cultural label for craziness, *loco.* As a *loco,* the individual would be much more severely stigmatized and considered to be out of control with little chance for recovery.

Although such conceptions may be important, other forms of cultural knowledge may also mediate attitudes toward the illness. For example, even Anglo-Americans who believe the problem to be a psychiatric condition called schizophrenia may nonetheless simultaneously believe that their relative is lazy (a culturally based personality attribution), and this might inhibit any possible recovery. That family views often combine broader cultural knowledge with more specific medical explanations points to the fact that these interpretations are complex and sometimes resilient in the face of attempts to modify them through psychoeducational programs offered by psychiatric professionals or advocacy groups (8). Estroff (78) has noted that schizophrenia is typically conceived of as an "I am" disease as opposed to an "I have" illness. The fact that Mexican-descent relatives conceive of schizophrenia as *nervios,* a legitimate illness that is outside the realm of personal control, may have a more salutary impact on personal identity that mediates the course and outcome of illness (21).

### *Cultural Meanings of Kin Relations*

Cultural meanings of family relations may differ along a continuum between a family orientation and an individualistic orientation. In cultures at one end of the continuum individuals may see themselves primarily as members of a larger kin-based social unit, behaving in ways that appear to maximize the family welfare relative to that of the individual. In cultures at the other end, individuals may consider family bonds secondary to the pursuit of their own personal goals and actions. Shweder and Bourne (79) conceptualized such differences in terms of sociocentric as opposed to egocentric definitions of the person. The sense of self in relation to others is important in family settings in outlining cultural preferences for affective and symbolic distancing. Although these formulations must be considered as ideal types, they nonetheless are important to determining different degrees of identification, involvement, and obligation that could in turn affect responses to a relative's illness.

In a study of schizophrenia in Ireland, Scheper-Hughes (77) found that patients were often harshly rejected and extruded from family settings. Ostracism by the family served to delimit the boundaries between self and others by condemning what was considered unacceptably deviant. The criticism and rejection also served to preserve the family identity as morally upstanding. Anglo-American relatives may more sharply delimit boundaries between the normal and the sick family members. For example, some Anglo-American relatives said that they had no personal experience or knowledge of their relative's problem and therefore could not "relate to" or identify with the relative (64). Behaviorally, this sometimes means that relatives feel quite uncomfortable spending much time together. Symbolically, the problem relative comes to be identified as unknown, foreign, and "other." This contrasts sharply with the family processes of identification among Mexican-descent relatives. Defining the problem as *nervios,* a common condition that in its milder forms afflicts nearly everyone, provides them a way of identifying with and minimizing the problem by claiming that the ill relative is "just like me, only more so" (66).

### *Identification of Cultural Rule Violations*

The behavior of individuals with schizophrenic illness can violate a host of cultural norms and proscriptions. This is perhaps why in some societies, such as those of the Javanese or the Pintupi aborigines of Australia, the same term is used for the mentally ill and for young children, indicating that such persons are not fully socialized (22, 75). Edgerton (74) has observed that although societies may allow for acceptable diversity in some human conduct, one knows "when the limits of acceptable variation have been exceeded because the result is 'trouble' in the form of complaints, disputes, accusations, recriminations, and the like" (p. 466). Critical comments may be viewed in this way—as complaints about the perceived violation of rules that people with schizophrenic illness may engage in with disquieting regularity. Shweder (80) underscored Freud's identification of "criticism (and related activities such as accusing and accounting) as the primary activity associated with rules." The criticism component of the expressed emotion research—which empirically makes up the lion's share of the construct—is valid for cross-cultural research if it is grounded in a generalizable definition of criticism as a negative response to cultural rule violations.

A limitation of previous analyses of critical comments is that researchers have considered that only two coding categories—symptom behaviors and enduring personality traits—can adequately inform a qualitative understanding of the nature of critical remarks. This analysis differs markedly from that developed for Mexican-descent and Anglo-American relatives, in which several additional coding categories became essential, and provides an example of the limitations of expressed emotion research in the absence of concern for indigenous perspectives (21). It is also reflective of North American ethnopsychology, since in the British and Anglo-American analysis (62), relatives' preoccupation with personality reflects the broader cultural and ethnopsychological concern about the importance of individual character traits. This analysis is not useful in the case of the Mexican-descent (and we would suspect Indian) relatives, where criticism of relatives on the grounds of personality defects is likely to be a less frequent occurrence.

This point serves to underscore how, in the absence of cross-cultural comparative analysis, science risks reification of our own cultural categories (54). In analyzing the content of critical comments, do we code the data from the perspective of the relatives who are motivated to make the critical comments or from the perspective of the analyst who codes it? The anthropological concern for the importance of perspective (the emic or indigenous categorization of meanings versus the etic or outside analyst's view) is crucial to the identification and interpretation of critical comments. This has yet to receive adequate attention, but we suggest that analysis of critical comments as complaints about cultural rule violations may provide a more productive basis for cross-cultural comparative analyses (4).

### *Vocabularies of Emotion*

Although mental disorder within the family may universally engender painful feelings among close kin, substantial differences exist with respect to the nature, intensity, and meaning of these affects. Relatives necessarily draw upon implicit cultural knowledge of which affects should be expressed and under which conditions they should be inhibited (17–20). Sanctions for and against the expression of certain emotions (such as anger manifest in criticism and hostility) exist as part of the culture's vocabulary of emotion (75). Whereas some societies (such as those of Tahitians or Inuit Eskimos) nearly always censure the expression of anger, others, such as that of the Kaluli of New Guinea, may require such expressions in particular settings (23, 81, 82). Cross-cultural variations in the vocabulary of emotion must play a part in the observed variations in expressed emotion profiles, as recorded for the British, Anglo-American, Mexican-American, and Indian studies.

## SUMMARY AND CONCLUSIONS

Attempts to conceptualize expressed emotion have thus far been largely restricted to a relatively microanalytic view of the characteristics of patients and relatives or their interactional qualities. These conceptualizations are based on personality, attributional, psychopathology, or social control factors. We argue here that these provide only partial understandings of expressed emotion and are primarily useful for intracultural analyses differentiating low and high profiles of expressed emotion. Such explanations do not shed sufficient light on the broader theoretical task of specifying the essential nature of the expressed emotion construct. Comparative research is essential for the theoretical grounding of this construct.

We think the general cross-cultural utility of the component elements of the expressed emotion index should be considered in ways similar to any other research construct, including schizophrenia and depression. These research and clinical constructs may be productively used in comparative research but should always be subject to cross-cultural scrutiny. They cannot be assumed to apply universally, but they may be usefully examined as a starting point. Substantial variation in expressed emotion profiles in different cultures and among different social classes is evidence against assumptions of a universally shared, psychobiologically given human response to schizophrenic illness. Instead, variation in expressed emotion profiles is more properly understood within the context of psychocultural and social variation in relatives' responses to a family member who suffers from schizophrenia. This variation is not limitless, however, and there may well be some features of response that are widely shared around the world.

We argue that the nature of expressed emotion (in the form of verbal criticism and emotional overinvolvement) is clearly grounded in cultural conventions; that is, it is culture specific. However, the cross-cultural presence of expressed emotion factors (criticism and emotional overinvolvement) is a matter for empirical investigation. Therefore, we must disagree with those who suggest that expressed emotion is necessarily ethnocentric or culture-bound. Some careful distinctions must be drawn here. Expressed emotion consists of two principal factors: critical comments and emotional overinvolvement. Without a doubt, the nature and meaning of criticism and emotional overinvolvement are culturally specific. However, it is not correct to assert that these basic elements of family interaction—criticism and emotional overinvolvement—are ethnocentric. They have definitively been found—in culturally specific ways—in the British, Mexican, and Anglo-American contexts, for example. It is our view that the main dimension of expressed emotion—verbal criticism—is likely to be found in some form and frequency in most of the world's cultures.

Yet another reason for focusing on the cross-cultural variations in expressed emotion profiles is the importance of addressing the concern of some family advocacy groups that the expressed emotion paradigm, rather than generating scientific knowledge, presumes that there are deficiencies in individual personalities and families. Even though this perception is in some cases apparently based on misunderstanding, individuals nonetheless feel blamed and responsible for their attitudes or actions (83). Expressed emotion, understood in cross-cultural perspective, can contribute toward a reflective understanding based less on an assumption of autonomous sentiments and actions and more on a constellation of shared features (19, 84).

Quite striking from a cross-cultural psychiatric point of view is the neglect on the part of expressed emotion researchers in calling for a systematic examination of the relationship between culture and expressed emotion. Since the anthropological and cross-cultural psychiatric literature of the past several decades has documented substantial cultural differences in conceptions of psychosis, display of emotion, behavioral rules and norms, and family structure and identification, it is reasonable to expect that features such as these are of key relevance to the explication of expressed emotion. In our view, it is these features that go to the very heart of what the construct of expressed emotion embraces.

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# Are Schizophrenia and Affective Disorder Related? A Selective Literature Review

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*Objective: Although most modern investigators accept the Kraepelinian view that schizophrenia and affective disorder are biologically distinct, others have suggested the psychoses are on a continuum of liability. This article is a selective review of evidence for the continuum model. Method: The author focuses on family, twin, and adoption data that do not support the Kraepelinian view of psychosis. Evidence characterized to a lesser extent includes the frequency of intermediate forms of illness (i.e., schizoaffective disorder), the inability to separate psychoses by classical symptoms into well-defined clusters, and the inability of laboratory measures to clearly define psychotic subgroups. Results: The data demonstrate that schizophrenia and affective disorder do co-occur in some families. Whether this co-occurrence reflects true overlap is unclear, and significant pathophysiological heterogeneity may underlie clinical continuity. In some recent studies the inclusion of nonmelancholic depressions in the affective illness category may have masked overlap. Conclusions: The author suggests that the Kraepelinian view of psychoses may need modification. Future research should focus on factors that may reveal overlap between schizophrenia and affective disorder: severity of schizophrenia and affective disorder in probands, severity of depression in relatives, the effect of the unipolar-bipolar disorder relationship on the co-occurrence of affective disorder and schizophrenia, and the relationship of nongenetic factors that might alter the clinical expression of a shared genotype. Also, investigators should not presume a dichotomy or continuum but should examine pure and mixed pedigrees and look for state- and trait-related endophenotypes, the convergence of which would provide the basis for focused molecular genetic study.*

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> It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect.
>
> —Kraepelin (1)

Most investigators and theorists studying schizophrenia accept the premise that schizophrenia is biologically distinct from affective disorder. The most compelling evidence supporting this Kraepelinian view of psychosis derives from family and twin data (2–4) that are interpreted as demonstrating little, if any, shared liability between the two major psychoses.

Despite this consensus, several theorists have proposed that schizophrenia and affective disorder are not distinct conditions but are, in fact, opposite ends of a continuum on which schizophrenia is the severest form and schizoaffective disorder is intermediate (5). Others have suggested a third alternative, that schizophrenia and bipolar affective disorder are two independent conditions and that unipolar and schizoaffective disorders are expressed in the relatives of patients in both categories (6). Evidence supporting these views also primarily derives from family and twin data, but it is considered weak or representative of idiosyncratic study groups, methods, or both.

The number and variety of studies which support the Kraepelinian view of psychosis exceed those which do not. A thorough review of that literature is not practical here. However, a detailed review of the data that suggest the accepted nosologic dichotomy may need to be modified has not been done, and such an exercise would be instructive. Nevertheless, critically reviewing the methodological shortcomings of these and pro-Kraepelinian studies is also beyond the scope of a journal article. Therefore, it is important to recognize that

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before 1980 no published family study met the criteria required of any modern study: prospective proband and relative selection, personal interviews, systematic data collection instruments, structured diagnostic criteria, and independent, blind diagnosis of probands and relatives. Most twin and adoption studies have similar problems. These deficiencies have been reviewed elsewhere (2, 7) and will be highlighted here only for illustration. Despite these problems, however, the literature is remarkably consistent in providing evidence that schizophrenia defined by most criteria is familial, that affective disorder is familial, and that in a significant minority of families the two psychoses co-occur.

## FAMILY STUDIES

### *Affective Disorder in Relatives of Schizophrenic Probands*

Rüdin (8), who worked with Kraepelin and who clearly accepted the dichotomous view of psychosis, presented family data in calculating the risk of a sibling's developing classical schizophrenia if another family member was mentally ill. Although the risk for schizophrenia was high (6.2%) if the ill relative was schizophrenic, it was higher if the ill relative had a nonschizophrenic (most often affective) psychosis (8.2%) or alcoholism (7.8%). If alcoholism and a nonschizophrenic psychosis were both present, then the risk for schizophrenia in other relatives was 22.7%. Further, although a sibling's risk for developing schizophrenia was high if the ill sibling was schizophrenic (6.2%), the risk for developing a nonschizophrenic psychosis was even higher (10.3%). Indeed, Rüdin found almost equal numbers of relatives with affective disorder and relatives with schizophrenia in the families of his schizophrenic probands.

Odegaard (9) gathered congruent data from Norway by using the family history method to assess relatives (N=824) but personally interviewing probands, making a final diagnosis only after at least a 5-year follow-up. Of 109 psychotic relatives of his "severe defect" schizophrenic probands, 78% were schizophrenic and about 15% were affectively ill. The disorders of another 7% were labeled "reactive psychosis," a popular concept in Scandinavia that McCabe (10) demonstrated has a familial relationship to affective disorder. Although appropriate population base rates are not available for comparison, nearly one-quarter of the psychotic relatives of Odegaard's schizophrenic probands could be considered affectively ill. Further, among the psychotic relatives of Odegaard's manic-depressive probands, 19% were diagnosed as schizophrenic (well above any known base rate), indicating the co-occurrence ran in both directions.

Penrose (11) studied all known families in which two or more members entered one of the Ontario mental hospitals during an 18-year period (5,456 affected pairs). He reported that, although schizophrenia and affective psychosis remained true to type in most families, "schizophrenia and affective psychosis are not very distinct entities and groups of closely related familial cases include both diagnoses." For example, of 184 subjects who each had at least one schizophrenic parent, 34 were diagnosed as having an affective disorder, whereas of 437 subjects who each had at least one manic-depressive parent, 205 were diagnosed as schizophrenic. Penrose's methods and diagnostic procedures, however, would not meet modern standards. Nevertheless, Karlsson (12) also observed both illnesses among the siblings of Icelandic and Californian schizophrenic probands, Reed and Hartley (13) found an excess of schizophrenia among all first-degree relatives of affectively ill U.S. probands, and Powell et al. (14) reported that manic-depressive Scottish parents had both manic-depressive and schizophrenic children, in the ratio of 3:2.

More recent family data are also inconsistent with the Kraepelinian dichotomy. For example, in their "Iowa 500" study, Tsuang et al. (15) concluded that their data "support the distinction between schizophrenia and affective disorders, although the distinction between schizophrenia and mania was not clear." The morbid risks for bipolar affective disorder in the first-degree relatives (personal and approximate interviews) of schizophrenic, manic, and depressed probands were 2.4%, 5.3%, and 3.0%, respectively, whereas the morbid risk for bipolar disorder in the first-degree relatives of comparison subjects was only 0.3%. Abrams and Taylor (7) also reported an excess of affective illness (6.9%) in the first-degree relatives of schizophrenic probands, but they included no group of subjects for direct comparison. Tsuang et al. also concluded that their data refuted the bipolar-unipolar affective disorder subtyping, and Taylor et al. (16, 17) also presented their own data and data from the literature questioning the unipolar-bipolar dichotomy. Logic suggests that if bipolar and unipolar disorders are, indeed, variations of the same process and that mania and schizophrenia are related in some way, then the clear Kraepelinian dichotomy is no longer tenable.

Similarly, Kendler et al. (4), reanalyzing the Iowa 500 data, reported that, compared to the relatives of comparison probands, the relatives of schizophrenic probands had a significantly higher risk for schizoaffective disorder (1.4%) and a difference in risk for bipolar disorder (1.2%) that approached statistical significance. Mendlewicz et al. (18) also reported a high risk for bipolar affective disorder (8.6%) in the first-degree relatives of schizophrenic probands, and Guze et al. (3), in an outpatient study, reported a questionable excess of primary depressive disorder (8.1%) in the first-degree relatives of schizophrenic probands than in the relatives of psychiatric comparison subjects (5.7%).

A number of studies, however, have not shown an increased risk for affective disorder among relatives of schizophrenic probands (19, 20) (see discussion that follows). In one such study, Coryell and Zimmerman (21) also failed to find a high prevalence of schizophrenia among relatives of any patient group when compared to relatives of normal subjects. Closer inspection of their data, however, reveals that of the six families of schizophrenic probands that had secondary cases of any major mental disorder, the secondary diagnoses were only affective disorders in three families and affective disorder and schizotypal personality disorder in a fourth family.

### *Schizophrenia in Relatives of Affectively Ill Probands*

The co-occurrence of schizophrenia and affective disorder also has been observed in families of affectively ill probands. For example, Angst et al. (22), in a large family study, also could not find support for the unipolar-bipolar dichotomy in their group of first-degree relatives of unipolar and bipolar probands. In addition, although base rates were not reported, among the first-degree relatives (N=617) of their bipolar probands (N=95), the morbid risks for schizophrenia and for schizoaffective disorder were higher than expected: 1.9% and 1.5%, respectively. The risk for schizophrenia among siblings was 2.5%, whereas among the probands' children it was 4.8%. In contrast, Loranger (23), who reported family history data for 200 manic probands, did not find a higher than expected risk for schizophrenia. However, in the Loranger study, the relatives' diagnoses were apparently made by persons who were not blind to the probands' diagnoses. In addition, in a large Swiss family study, Scharfetter and Nusperli (24) compared morbid risks for schizophrenia in the first-degree relatives of schizophrenic and affectively ill probands and found them to be 8.9% and 3.3%, respectively. Although relatives of normal subjects were not included for comparison, the risk for schizophrenia in relatives of other normal subjects diagnosed by similar criteria (*ICD-9*) is about 0.6%, suggesting the risk in the relatives of the affectively ill probands in the Scharfetter and Nusperli study is significantly higher than expected. Smeraldi et al. (25) examined the relatives of affectively ill probands in Lombardy and observed a higher than expected risk for Feighner-defined schizophrenia in the siblings of unipolar, but not bipolar, probands. Lastly, in the Iowa 500 study (15), in which the risks for bipolar affective disorder were similar in the relatives of schizophrenic and bipolar probands, the risks for schizophrenia in these relatives were also similar and statistically greater than the risk for schizophrenia in the relatives of normal comparison subjects. The morbid risks for schizophrenia in the relatives of schizophrenic, manic, and normal probands (personal and approximate interviews) were 5.5%, 3.2%, and 0.6%, respectively. The risk for schizophrenia in the relatives of depressed probands was 1.7%.

Nevertheless, failure to find an excess of schizophrenia in the first-degree relatives of manic-depressive patients has been reported many times (4, 26, 27). However, in an extension of one of these studies (4), Kendler et al. (28) did find an excess risk for schizophrenia (4.3%) in the first-degree relatives of probands with "psychotic affective disorder." In fact, the risk for schizophrenia in these families was higher (although not statistically significant) than the risk for schizophrenia in the families of schizophrenic probands (3.7%). The morbid risk for affective disorder in the relatives of these probands was also much higher (20.0%) than base rates, suggesting that severity of proband illness may account for some of the discrepancy among studies assessing the morbid risk for schizophrenia in the relatives of affectively ill probands. Indeed, in a separate analysis (29) of the same data base, the same authors estimated the risk for schizophrenia in the relatives of bipolar patients with psychotic symptoms to be 2.5%, compared to 1.0% in relatives of normal comparison subjects ($p<0.05$). These figures were separate from those for schizoaffective disorder (1.4% versus 0.1% for normal subjects) and atypical psychosis (2.5% versus 0.3% for normal subjects), which were also higher in the relatives of schizophrenic probands. Tsuang et al. (29) stated, "If affective disorder with psychotic symptoms is not included as a subgroup of major affective disorder, then the results, based on familial data, support the rationale behind the nosological distinction between DSM-III schizophrenia and major affective disorders."

However, it seems more reasonable to conclude not that the data should be excluded but, rather, that the nosology should be modified. Tsuang et al. (29) further stated, "It may be possible that some affective disorders with psychotic symptoms could be a genetic variant of schizophrenia." But they then concluded, "Therefore, including all affective disorders with psychotic symptoms in the category of DSM-III major affective disorder may lead to over-diagnosis of affective disorders."

Finally, in a series of studies, Gershon et al. (6, 30) also assessed the risks for affective disorder and for schizophrenia in the first-degree relatives of schizophrenic and affectively ill probands. Relatives of schizoaffective and normal probands were also assessed. In their 1982 study (30), these authors found a familial relationship between schizoaffective and affective disorders, whereas in their 1988 study (6), they found a familial relationship between schizoaffective disorder and schizophrenia. These findings led to their hypothesis that there are two distinct psychoses, schizophrenia and bipolar affective disorder, and that unipolar and schizoaffective disorders are somehow related to both. Crow (5) reviewed these studies and concluded that the data just as strongly suggested a continuum from affective disorder through schizoaffective disorder to schizophrenia. The morbid risks for bipolar and unipolar disorder found by Gershon et al. (6) in the first-degree relatives of schizophrenic probands (2.2% and 14.7%, respectively) were two to three times those of the relatives of normal subjects (0.8% and 6.7%, respectively). Gershon et al. also found that the relatives of chronic psychotic patients who had abused drugs had a morbid risk for unipolar disorder of 18.8%. Coupled with findings of associated birth complications (31, 32) and prenatal viral exposure (33) among schizophrenic patients, these data are consistent with the expression of liability along a continuum from affective disorder through schizoaffective disorder to schizophrenia, depending on the degree of liability and the exposure to various neurologically damaging factors.

## TWIN AND ADOPTION STUDIES

Data from twin and adoption studies have frequently been cited as support for our present nosology (2). Nevertheless, some twin and adoption data do not fit this dichotomous classification. For example, the London twin study by Slater and Shields (34) provides classic evidence for a genetic predisposition to schizophrenia; the concordance rates for monozygotic and dizygotic twins were 65% and 14%, respectively. However, Slater and Shields also found that among the siblings of schizophrenic patients in the index twin pairs the prevalences of affective disorder and schizophrenia were similar and that they had more parents with affective disorder than with schizophrenia (16 versus 12 individuals). Subsequent reports of sets of twins (35, 36) and triplets (37) with schizophrenic and affectively ill individuals also suggest some relationship between the two psychoses, as do reports of pedigrees in which the two illnesses co-occur (38). This co-occurrence is best illustrated by Farmer et al. (35), who applied *DSM-III* criteria to twins from the Maudsley schizophrenic twin series. Farmer et al. studied 24 monozygotic and 33 dizygotic twin pairs in which at least one member was originally diagnosed as schizophrenic and for which the original concordance rates for schizophrenia were 42% and 9%, respectively. Five monozygotic schizophrenic probands were found to have a co-twin with a *DSM-III* affective disorder, and a sixth had a co-twin diagnosed as having either schizoaffective or bipolar II disorder. A seventh index twin, rediagnosed as having schizophreniform disorder (criteria identical to those for schizophrenia except no duration criterion), had a co-twin diagnosed as having depression. Thus, seven of 24 monozygotic twin pairs had one member with a schizophrenic syndrome and the other member with an affective syndrome. Six pairs remained concordant for schizophrenia. Farmer et al. concluded that the problem may lie with the *DSM-III* criteria, but it is equally plausible that these data indicate some shared liability among some subgroups of patients with schizophrenia and affective illness.

Similar problems in deciding whether the data indicate poor diagnostic specificity or shared liability emerge from some of the adoption literature. For example, in the Danish adoption study (39), of 69 biological parents of index schizophrenic adoptees, 10 were considered to have acute schizophrenia (a short, rapidly developing psychosis with intact affect) or schizoaffective disorder; both of these categories are considered, by some investigators, to be variations of affective disorder (40). Eight parents were also diagnosed as borderline, and nine were given doubtful diagnoses of schizophrenia or schizoid personality. Further, among the schizophrenic adoptees, rediagnosis identified only three patients with unequivocal (i.e., chronic) schizophrenia (41). Thus, although adoptees are similar to their biological parents and their biological parents have more illness than do normal comparison subjects, this pattern is best demonstrated for a spectrum of psychotic syndromes, rather than for the classic Kraepelinian dementia praecox.

## OTHER EVIDENCE

In addition to familial studies, problems with the Kraepelinian dichotomy derive from three other areas: 1) intermediate forms, particularly schizoaffective disorder, are common; 2) there is no clear separation of the psychoses by classical symptoms into well-defined clusters; and 3) laboratory measures, while delineating psychotic from nonpsychotic patients, have not clearly defined psychotic subgroups.

First, if the Kraepelinian dichotomy is valid, intermediate forms (usually lumped into the category schizoaffective disorder) should be uncommon. It is difficult, however, to precisely determine the prevalence of this intermediate group because correlations between definitions of schizoaffective disorder are poor (42), making generalizations difficult. Nevertheless, Brockington and Leff (42) found that 8% of hospitalized psychotic patients met three of eight definitions, and Surtees and Sashidharan (43), using the Research Diagnostic Criteria (RDC) to study community samples, found that 5.7% of the adult subjects who received psychiatric diagnoses had schizoaffective disorder, and this rate is similar to that found for schizophrenia. Johnson (44) also reported that one-half of untreated new acute schizophrenic patients and about one-third of chronic schizophrenic patients were depressed. Their depression was defined as "clinically meaningful and likely to provoke some treatment," and they each scored 15 or higher on the Hamilton Rating Scale for Depression. Montgomery (45) reported a similar prevalence of depressive symptoms in schizophrenic patients meeting the criteria of the 1977 NIMH Diagnostic Interview Schedule (DIS) and the Present State Examination.

All current concepts and definitions of schizoaffective disorder combine in some way affective symptoms with other features thought to be associated with schizophrenia (e.g., certain kinds of hallucinations and delusions). Studies of these phenomena, however, clearly demonstrate that these schizophrenic-like features occur with high frequency among patients with affective syndromes (46). For example, first-rank symptoms, used to define schizoaffective disorder in the RDC, appear to occur in 15% to 20% of patients with acute mania, whereas persecutory delusions and auditory hallucinations, used to define schizophrenia and schizoaffective disorder in *DSM-III* and *DSM-III-R*, occur in over one-third of the patients with acute mania (47, pp. 15–55). These figures suggest that somewhere between 25% and 30% of manic patients could, by several standards, be considered to have schizoaffective disorder or a cross-sectional clinical picture intermediate between those of "pure" schizophrenia and affective disorder. Although some (see review, 40) have argued that schizoaffective disorder is simply a more severe form of affective disorder, others have suggested that these patients have either a third type of psychosis (48) or a variation of schizophrenia (49). Still others (50) have concluded that the data do not fully support any of these views, that the label "schizoaffective" simply means diagnostic uncertainty, and that this patient group is heterogeneous. The lack of consensus suggests that the ultimate conclusion about the nature and extent of schizoaffective disorder will to a large degree determine the boundary between schizophrenia and affective disorder. The unclear delineation of schizoaffective states and their considerable prevalence weakens the case for the Kraepelinian dichotomy.

More damaging to the Kraepelinian dichotomy is the work of Kendell and associates (51–53). Kendell and Gourlay (51, 52) tried to discriminate affective disorder from schizophrenia on the basis of various features thought to be characteristic of each disorder. They were unable to do so, finding a unimodal distribution of symptoms, rather than the bimodal distribution required by the Kraepelinian model. Other investigators have also observed this unimodal distribution (54) or have obtained ambiguous results (55, 56). Kendell and Brockington (53) further assessed the putative boundary between affective disorder and schizophrenia by examining the relationship between symptoms and outcome in 232 psychotic patients; the dichotomy predicted a nonlinear relationship. Such a relationship was not apparent.

In contrast with the several studies in which a clear symptom distinction between schizophrenia and affective disorder could not be demonstrated is the study by Cloninger et al. (57), who assessed the putative distinction by a series of discriminant analyses of symptoms observed in a large group of outpatients and their ill relatives. Cloninger et al. found a point of rarity and concluded that their data fit the Kraepelinian model, but they pointed out that because the clinical features used to establish the point of rarity did not include emotional blunting or negative features, their findings might not be applicable to hospitalized or chronic (hebaphrenic) patients.

Last, although the psychoses are associated with abnormalities in brain structure (47, pp. 503–540; 58; 59) and function (47, pp. 416–488, 541–595), none of these abnormalities is pathognomonic, and many are observed in both patients with schizophrenia and patients with affective disorder. For example, the degrees and prevalences of soft neurologic signs (about 70% in each psychosis) (60), structural brain abnormalities (10%–30% in each psychosis) (47, pp. 503–540; 58; 59), and neurotransmitter system aberrations (47, pp. 416–458; 61) in schizophrenia and affective disorder are more similar than dissimilar.

Particularly striking are the data on structural brain abnormalities in psychotic patients. Since the presentation by Johnstone et al. (62) of CT scan findings characterizing some schizophrenic patients as having some (not necessarily clinical) degree of cortical atrophy and ventricular enlargement, the specificity of these findings to schizophrenia has been assumed by some investigators. Thus, much of the brain imaging literature now focuses on whether the schizophrenic patients with CT abnormalities represent the genotype or the phenocopy of schizophrenia. Although a full review of this literature is beyond the scope of this paper, it is clear that the structural brain abnormalities observed in some schizophrenic patients are not specific and are also observed in manic patients and depressed patients.

For example, of the more than 40 studies (58, 59) measuring the lateral ventricle system in schizophrenic patients, over three-fourths demonstrated significantly larger ventricles in these patients (6% to 40% of patients) than in various comparison groups. Larger ventricles did not correlate with greater age (63), suggesting little structural change over time, but did correlate with greater illness severity, social impairment, and cognitive dysfunction. Ventricular enlargement has also been observed in the ill members of monozygotic twin pairs discordant for schizophrenia (64). Other findings in schizophrenic patients include third ventricle enlargement, cortical gyri shrinkage (particularly frontotemporally), cerebellar atrophy (5%–17% of patients) (58, 59), cerebral hemisphere asymmetry, and thickening of the corpus callosum. Although there have been relatively few MRI studies of schizophrenia, and some of those studies have not shown differences between schizophrenic and normal comparison subjects (65), most have shown patients to have smaller frontal lobes and cerebral size and complex density (T1) abnormalities in several brain regions (58, 66, 67). Similar MRI abnormalities have also been reported in the schizophrenic twins in discordant monozygotic pairs (68).

Strikingly similar brain structure abnormalities have also been observed in patients with affective disorder. For example, numerous CT studies of manic patients have shown them to have enlarged lateral ventricles (69, 70), frontotemporal sulcal widening, and cerebellar atrophy (71, 72). As with schizophrenia (58, 59), a few studies did not show these abnormalities (70). As yet, clinical correlates have not been established. Depressed patients, particularly those with psychotic features (73), high cortisol levels (74), and greater severity and poor outcome (75), also have ventricular enlargement and frontotemporal sulcal widening.

Abnormal T1 values shown by MRI scans have also been reported in bipolar patients (76, 77), and these resolved somewhat after treatment with lithium. Ventricular enlargement in some depressed patients has also been reported to resolve with clinical improvement (74), as is the case in some patients with cerebral atrophy secondary to therapeutically or pathologically related hypercortisolism (78). MRI studies have also demonstrated smaller than normal frontal lobes in bipolar patients and elderly depressed patients (58, 59). Bipolar patients have also been found to have abnormally small temporal lobe volumes (79), and depressed patients have been found with

MRI to have small caudate volumes (80). This pattern is particularly similar to the MRI T1 findings in some schizophrenic patients (81).

Although there are significant similarities between the CT/MRI findings in schizophrenia and affective disorder, there is some evidence that the abnormalities in schizophrenia occur early in the course of the illness and do not appreciably change over time, whereas the abnormalities in affective disorder occur later and may fluctuate with the clinical picture. These similarities and differences could result from 1) different pathophysiologies with a common structural pathway or 2) a process resulting from some shared liability that, as with the signs and symptoms of the two syndromes, is expressed differently in schizophrenia and affective disorder. Jeste et al. (82), in an extensive review of this literature, reached similar conclusions and suggested that neuropathological studies (rare in patients with affective disorder) would need to be done to resolve this issue.

Also of interest are the data related to dexamethasone suppression test results for schizophrenic patients. Although it is now felt to be an epiphenomenon without etiologic significance, dexamethasone nonsuppression has been strongly associated with affective disorder, particularly melancholia (i.e., it was reported to have high specificity and sensitivity). However, in his review and meta-analysis of data from this literature, Veragoni (83) found that 26% of schizophrenic patients were nonsuppressors, significantly more than the 5% among normal subjects. Further, Tandon et al. (84) found that 39% of unmedicated patients with RDC/*DSM-III* schizophrenia were nonsuppressors and that nonsuppression was related to negative but not depressive symptoms (as rated with the Scale for Assessment of Negative Symptoms and Hamilton depression scale, respectively). In addition, Altamura et al. (85) studied 54 patients with *DSM-III* schizophrenia divided into positive and negative symptom subtypes and found that 40% overall and 62% of the negative symptom group were nonsuppressors. This last figure is higher than that reported for melancholic patients (50%).

The degree of overlap among studies of biological variables is such that Meltzer (86), reviewing this literature, concluded a continuum was a reasonable interpretation of the data. Consistent with these biological similarities is the fact that, although schizophrenic patients as a group have a worse outcome than do patients with affective disorder, when these two groups are combined with schizoaffective disorder patients the overlap among the three groups is significant and suggests a unimodal distribution (87–89). Also, similar biological treatments (e.g., neuroleptics, ECT, anticonvulsants, lithium [90]) are of benefit to patients in each diagnostic category. Finally, follow-up studies (91, 92) show that, although most patients experience the same form of illness during follow-up periods, some experience early episodes of affective disorder followed by episodes of schizophrenia (about 10%), or vice versa (about 5%). In some earlier studies the diagnostic criteria were poor and the diagnoses of schizophrenia were probably erroneous, but the changes in illness form noted in the more recent studies are not due to changes in diagnostic system, as the same criteria were applied throughout.

## DISCUSSION

This review is selective, i.e., primarily presenting studies which are consistent with the idea that there is a relationship between some forms of schizophrenia and of affective disorder. Nevertheless, on the basis of them it seems justifiable to conclude that data from these family and twin studies and, to a lesser extent, some adoption studies demonstrate that schizophrenia and affective disorder co-occur in some families. However, is this co-occurrence significant, and does it indicate overlap?

Certainly, most investigators have not concluded that there is significant overlap (2). How can that view be reconciled with the findings I have reviewed? First, in some of these "negative" studies (4, 29), co-occurrence was in fact observed but the investigators did not address their findings. In others (93), no mention of co-occurrence was made, and, as at least base rates should have been observed, perhaps the investigators did not look for co-occurrence. In addition, some studies that did not show significant co-occurrence had substantial methodological problems. For example, the study by Pope et al. (94) was based solely on chart information, and Loranger's study (23) was limited by family history information obtained only from charts, lack of a comparison group, relatives' diagnoses that were made by persons who were not blind to proband diagnosis, and diagnoses of only the ill relatives who had received treatment. Nevertheless, in several studies (19, 95) the methods were good and the group sizes were adequate, and no significant co-occurrence was observed. These studies, coupled with those which showed significant co-occurrence, suggest a complex pattern of heterogeneity: some psychoses appear to be on a continuum of liability, whereas other psychoses with similar signs and symptoms have different and distinct etiologies.

For such a complexity of relationships, significant and varied environment-gene interactions are likely. For some patients these interactions would be unique, i.e., if they had a specific genotype independent of the genotypes for other psychoses (see review, 96). For schizophrenic patients and patients with affective disorder who share a genotype, the shared genotype could be for a propensity for psychosis. Environmental factors would largely determine whether the vulnerable individual would be unaffected, affectively ill, schizoaffective, or schizophrenic. Winokur (97) has suggested this model for the affective disorders, but it could apply equally well to a schizophrenia-affective disorder continuum. Environmental factors that have been studied as possible influences on the expression of psychosis include gestational and perinatal CNS damage (31, 32), childhood head trauma (98), prenatal CNS viral infection (33), and drug abuse (99). The size, site, and precise timing of the lesions induced by these environmental factors have differential, important effects on genes (100) and on neuronal cell migration and pruning during development, and they may not be manifested until sexual maturity. Thus, the degree of pathophysiological heterogeneity underlying the psychoses could be extraordinary, even if some forms of psychosis have a common genotype.

Another argument against overlap between schizophrenia and affective disorder derives from studies of dual matings, i.e., cases in which one parent is schizophrenic and the other has affective disorder, or both parents have either schizophrenia or affective illness (2, pp. 89–93). These studies do not indicate that the psychotic offspring of one parent who is schizophrenic and one who is affectively ill have mixed psychoses, as one might expect if the parents' different clinical pictures resulted from similar liabilities, which could be expressed as "pure" or as intermediate forms. In most cases, parents who are both diagnosed as schizophrenic do not have both manic-depressive and schizophrenic offspring. However, dual matings are rare (but patients with mixed symptoms, i.e., schizoaffective disorder, are not), the diagnostic criteria in these studies were poor or nonexistent, and the diagnoses of the offspring were usually not made by persons who were blind to the parents' diagnoses. Further, it has not been demonstrated that schizophrenic and affectively ill patients can be clearly separated by symptoms or biological variables or, when they are combined with patients with schizoaffective disorder, that there is a clear separation of the psychoses by long-term outcome or specificity of treatment response. The removal of patients with schizoaffective disorder from studies designed to demonstrate the separation of schizophrenia from affective disorder may have been justified at one time in the search for the simplest answer to the nature of the psychoses, but this strategy has not been successful and continued exclusion may be artificial and judgmental.

Although schizoaffective disorder constitutes between 10% and 30% of functional psychoses (depending on the criteria one uses), it is unclear how many schizophrenic patients have family histories of affective disorder and how many affective disorder patients have family histories of schizophrenia. In one study that examined the first part of this relationship (92), of 135 patients diagnosed as schizophrenic (most of whom met *DSM-III* criteria), about 20% had family histories of either unipolar (13.3%) or bipolar (7.5%) affective disorder. The diagnosis of these probands, however, was unclear because during a variable follow-up period 70% of those with family histories of bipolar illness, 66% of those with family histories of unipolar disorder, and 40% without any family history of affective disorder had subsequent episodes of affective illness.

It is also unclear what the morbid risks are for schizophrenia and affective disorder in the first-degree relatives of probands with these diagnoses. From my review, it appears that the risk for schizophrenia among the relatives of probands with affective disorder is between 0.5% and 3.5%, whereas the risk for affective disorder in the first-degree relatives of schizophrenic probands is about 6% to 8%.

Are these risks higher than those of the general population and, therefore, suggestive of shared liability? Certainly, the risk for schizophrenia in the first-degree relatives of affective disorder probands is not overly impressive, and most studies have not shown a high risk. Most family studies of affective disorder, however, did not address the risk for schizophrenic disorder in relatives. If some psychoses are on a continuum, the risks in relatives of affective disorder probands might be expected to be only slightly higher than expected for schizophrenia, high for affective disorder, and somewhere in between for schizoaffective disorder. For the relatives of schizophrenic probands, the risk for schizophrenia might be high, but the risks for schizoaffective and affective disorders would also be high. There is some evidence consistent with these expected patterns. For example, although most studies of schizophrenic subjects did not assess intermediate forms of psychosis (i.e., schizoaffective disorder), several studies (4, 21, 27, 29) did so and showed that the risk for schizoaffective disorder was higher than average (about 2%) in the first-degree relatives of schizophrenic probands. Other studies (21, 22, 30) have demonstrated a high risk for schizoaffective disorder (about 2%–3%) in the first-degree relatives of affective disorder probands. There are 14 published family studies of schizoaffective disorder (see reviews: 40, 101, 102) with apparently adequate numbers of probands (more than 40) and adequate methods. Among these, the mean risks in relatives for schizophrenia, schizoaffective disorder, and affective disorder were 3.72%, 5.30%, and 15.68%, respectively.

Whether the risk for affective disorder in the relatives of schizophrenic probands is higher than expected remains unclear and may ultimately be determined by what depressive syndromes are included in the affective disorder category and the resulting conclusion as to the population risk for affective disorder. The present-day practice of including nonmelancholic major depression and dysthymia in the category of affective disorder leads to population risk figures of about 6% (103, 104), although some investigators reported much higher risks (105). However, using the European, narrower view of depression, Slater and Cowie (106) estimated the risk for manic-depressive illness to be closer to 1%. Eastwood et al. (107) reached a similar conclusion on the basis of the prevalence of lithium treatment in metropolitan Toronto. If the lower figure is accurate, then the risks for affective disorder in the first-degree relatives of schizophrenic probands in several studies are clearly higher than expected. Hallstrom's Swedish study of depression (108) used *DSM-III* criteria and showed a population prevalence of 6.9% for all major depression but only 2.9% for melancholia. If depression is heterogeneous, as suggested by several studies (109, 110), then it is important to determine whether it is the melancholic variety that co-occurs in relatives of some schizophrenic probands and whether that prevalence is greater than that of the general population.

It is also important to recognize that much of the present-day information on population risk was derived with controversial methods. For example, many studies (111, 112) used lay interviewers who administered the DIS, a structured interview instrument with only modest reliability and low sensitivity for depression, schizophrenia, and mania (respective kappas=0.63–0.68, 0.51–0.60, 0.63–0.66; sensitivities=71%–80%, 50%–70%, 65%–75%). Independent assessments of the DIS (113) suggest that prevalence estimates based on its use with lay interviewers are significantly different from those based on the standard psychiatric diagnosis and that subjects identified as cases by the two methods often differ. The kappas were also low for major depression (0.25), schizophrenia (0.19), and mania (0.09). Further, estimates of depressive illness in some studies were so high that they call into question the clinical meaningfulness of the behavioral clusters labeled "depression." For example, in a study of children at high risk for depression, Weissman (114) found that among the children of the nondepressed, normal comparison parents, 13.4% had major depression, 14.9% had dysthymia, 13.4% had conduct disorder, and 17.9% had anxiety disorder. Over 50% of the children from *normal* households were identified as psychiatrically ill. All these data suggest that the Kraepelinian view of the psychoses may need to be modified. This dichotomy does not account for data from a number of family and twin studies, nor can it be clearly demonstrated from clinical and laboratory data. Further research in all these areas is essential, and studies should be designed without preconception and include patients with various forms of psychoses. Research should also focus on the factors that may account for differences across studies, e.g., number of subjects, severity of schizophrenia and affective illness in probands, severity of depression in relatives, the effect of the unipolar-bipolar affective disorder relationship on affective disorder in relatives of schizophrenic probands, and nongenetic factors (street drugs, perinatal problems, viral disease) that might alter the clinical expression of a shared genotype.

Continued maintenance of an unmodified Kraepelinian, dichotomous view of psychosis, given the data from the studies reviewed here, requires some speculation. For example, it could be argued that the manipulation of typical cross-sectional and longitudinal clinical information in studies failing to show clear clinical clusters is fruitless, because the two putative diseases differ on clinical dimensions orthogonal to the clinical features usually studied. What these other features might be is unclear. Perhaps it would prove helpful to focus on social, interpersonal, and neuromotor behaviors that have been reported to be odd in some psychiatric patients (115–117) but are not classifiable into traditional psychopathological categories.

Another alternative could be that there are two distinct illnesses but (like some cancers) they share so many of the same cross-sectional and longitudinal clinical features that their distinction can only be observed through laboratory measures. However, present laboratory technology has not provided evidence for this clear distinction of the psychoses. The application of hypothesis-generated laboratory measures to pure and mixed pedigrees to determine state- and trait-related endophenotypes might provide support for this alternative defense of the Kraepelinian dichotomy.

An alternative to the continuum model that is also inconsistent with the Kraepelinian dichotomy is the view that there is significant pathophysiological heterogeneity among the psychoses (118). To explain the data, however, this heterogeneity would have to be on the order of what is observed among the mentally retarded. Although mental retardation is clearly associated with multiple pathophysiological processses and determinants of those processes, it is defined by similar performance on certain tests. For the psychoses, they may also derive from multiple pathophysiological processes and determinants but are categorized loosely together because of certain behaviors (hallucinations, delusions, aberrations in affect) shared by all, so their underlying heterogeneity is obscured.

As none of these possibilities can be clearly discarded, future studies of the pathophysiology or determinants of psychosis should not presume a single model. Thus, future research either should focus on the neurology of specific psychopathological phenomena (the study of which transcends the discrete disease issue) or, if focusing on disease entities, should have a flexible design. The strategies of extensively studying pure or mixed pedigrees and studying people at high risk for psychosis appear to be the most powerful approaches (119, 120), ultimately applying focused molecular genetic techniques to pedigrees with converging biological data. Whether these techniques will be as successful for the psychoses as they have been for many nonpsychiatric diseases remains to be established.

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# Should Caffeine Abuse, Dependence, or Withdrawal Be Added to *DSM-IV* and *ICD-10?*

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Objective: *The authors reviewed basic science and clinical data on caffeine abuse, dependence, and withdrawal in order to make a conclusion about whether these disorders exist and should be included in* DSM-IV *and* ICD-10. Method: *Studies were located through computerized searches, reference sections of published articles, and written requests.* Results: *The studies show that abstinence from caffeine induces a withdrawal syndrome of headache, fatigue, and drowsiness which begins within 12–24 hours and lasts about 1 week. The syndrome can be severe and appears to be one reason for continued use of coffee. The prevalence of this caffeine withdrawal syndrome is unknown. Use of caffeine may aggravate some common behavioral and medical disorders. In double-blind tests, a subset of coffee and soda drinkers reliably self-administered caffeinated beverages in preference to uncaffeinated beverages. Clinical indicators of dependence, such as difficulty stopping use of caffeine and use despite harm, have not been documented.* Conclusions: *Caffeine withdrawal but not caffeine abuse or dependence should be included as a diagnosis in* DSM-IV *and* ICD-10. *Future research should focus on whether some caffeine users exhibit clinical indicators of drug dependence.*

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Caffeine is the most widely used drug in the world. For example, over 85% of Americans ingest caffeine daily, and the average caffeine intake is approximately 200 mg/day (1, 2). Excessive caffeine intake is especially prevalent among psychiatric patients (3–5); 22% of psychiatric inpatients use more than 750 mg/day (5), compared to 9% of the general population (2). Caffeine can be ingested from brewed coffee (100 mg/6 oz), instant coffee (65 mg/6 oz), tea (40 mg/6 oz), soda (50 mg/12 oz), and over-the-counter analgesics, antihistamines, stimulants, and weight-loss aids (50–200 mg/tablet). Whether caffeine is a drug of abuse or dependence and whether cessation of caffeine use can induce withdrawal symptoms have been examined in previous reviews (6–8); however, none of these has discussed caffeine use disorders in the light of *DSM* or *ICD* criteria.

Many definitions of and criteria for drug abuse, dependence, and withdrawal have been proposed. To increase the comprehensiveness of this review, broad definitions of these terms are used. "Withdrawal" refers to time-limited effects due to cessation (9). Drug tolerance is usually associated with withdrawal (10). "Abuse" refers to harmful or hazardous use (*ICD-10, DSM-III-R*) or use for socially disapproved reasons (10). "Dependence" refers to a constellation of symptoms outlined by Edwards and colleagues (11, 12), *ICD-10*, and *DSM-III-R* that includes withdrawal, tolerance, and abuse. "Dependence" in these schemas also focuses on loss of control over drug use, excess time in procuring or preparing the drug, progressive neglect of self because of drug use, narrowing of the pattern of drug use, and rapid reinstatement of drug dependence upon relapse.

## CAFFEINE WITHDRAWAL

### *Basic Science Criteria*

The *DSM-III-R* definition of withdrawal is "development of a substance-specific syndrome that follows the cessation of, or reduction in, intake of a psychoactive substance that the person previously used regularly" (p. 118).

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Other criteria include demonstration of relief of the syndrome by the readministration of the drug, rebound or "overshoot" effects, and physical changes (9).

*Experimental induction of withdrawal symptoms.* Six studies have examined caffeine deprivation in nonhuman subjects chronically treated with caffeine (13, 14). Most found that deprivation of caffeine decreased locomotor activity or disrupted performance to below baseline levels (13, 14). We are unaware of studies of changes in physiological, hormonal, or biochemical processes in nonhuman subjects.

In over 14 experimental trials with human beings, headache, decreased arousal, and fatigue consistently occurred upon cessation of caffeine use (14). These symptoms occurred during well-controlled, blind deprivation of caffeine alone (e.g., substitution of decaffeinated coffee) and were reversed by readministration of caffeine. Several other withdrawal symptoms have been reported, including anxiety, nausea, and craving for caffeine, but these have not been as well documented (14). Caffeine withdrawal symptoms begin 12–24 hours after deprivation, peak at 20–48 hours, and last about 1 week (14). One study (15) showed that in some coffee drinkers, withdrawal symptoms reliably occurred with repeated substitutions of decaffeinated coffee (i.e., on five or six of six tests).

Cessation of caffeine also has biochemical and physiological effects, such as increased blood pressure (16), 3-methoxy-4-hydroxyphenylglycol (MHPG) (17), and heart rate orientation response (18) and decreased β-adrenoreceptor sensitivity (19). Other studies have failed to find effects of caffeine deprivation on biochemical and physiological measures such as blood pressure (20), levels of catecholamines (20), heart rate (20), and muscle tension (21).

Several studies (18, 22–24) have shown decreases in performance on vigilance and psychomotor tasks after subjects stopped using caffeine. In addition, in most of the studies which have shown that acute doses of caffeine can improve performance, subjects have been deprived of caffeine for 12 hours. Thus, these studies may have been demonstrating reversal of withdrawal effects rather than direct effects of caffeine (25).

Factors predisposing to withdrawal symptoms have not been well studied. Two experimental studies (26, 27) reported that the severity or probability of withdrawal effects is related to the maintenance dose of caffeine, but other studies (15, 24) did not find this. In two studies (27, 28), withdrawal symptoms occurred at doses of caffeine as low as 100 mg/day.

One case report (29) suggested that neonatal withdrawal symptoms could occur after heavy maternal caffeine intake; however, empirical studies are lacking. In addition, neonatal withdrawal symptoms have not been found with maternal use of other stimulants (e.g., cocaine, amphetamine, and nicotine).

Several mechanisms could account for the symptoms of caffeine withdrawal: greater sensitivity to endogenous adenosine (caffeine is an adenosine antagonist) (30), changes in adrenergic sensitivity (19), or, in the case of headaches, increased cerebral blood flow (31). Although there are some data supporting these mechanisms, the data are not yet convincing.

*Tolerance.* Tolerance is usually associated with withdrawal. Tolerance is defined in *DSM-III-R* as the "need for markedly increased amounts of the substance (i.e., at least a 50% increase) in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount" (p. 168). The working draft of *ICD-10* has a similar definition.

Several studies (32–34) have documented tolerance to the effects of caffeine in nonhuman subjects. In addition, repeated dosing of caffeine in nonhuman subjects increases the number and sensitivity of brain adenosine receptors, which might be a mechanism for the development of tolerance (35, 36).

In humans, experimental administration of caffeine induces tolerance to hemodynamic and other physiological effects of caffeine (20). An experimental demonstration of tolerance to the behavioral effects of caffeine in humans has not been reported. Previous studies have indicated that caffeine has fewer negative subjective effects in persons who drink large amounts of coffee than in those who drink small amounts (37–40); however, whether this is due to acquired tolerance or to self-selection by individuals differing a priori in sensitivity to caffeine is unclear. Finally, studies linking the degree of caffeine tolerance and that of caffeine withdrawal symptoms have not been reported.

### *Clinical Criteria*

*Severity of withdrawal symptoms. DSM-III-R* states that caffeine withdrawal was not included because "although the existence of a caffeine withdrawal headache is well established, the syndrome is usually not severe enough to warrant clinical attention" (p. 138). However, several double-blind, placebo-substitution trials have documented the occurrence of caffeine withdrawal headache, drowsiness, or fatigue that interfered with normal function and was at times incapacitating. In the first report (41), 22 men were given 600–750 mg/day of caffeine for 6–7 days, and then placebo was substituted. On 21 (55%) of 38 trials, headache "as severe as the subject had ever had" was reported. In six (27%) of the subjects, the headache was consistently accompanied by some degree of nausea, and vomiting occurred in two (9%) of the subjects.

In four more-recent studies, decaffeinated coffee was substituted for caffeinated coffee in a double-blind manner. In the first study of six heavy coffee drinkers (22), on six (10%) of the 63 tests the headache was rated as strong. In a second study of moderate coffee drinkers (24), severe headaches were reported on eight (15%) of 55 trials, severe drowsiness on nine (16%) of the trials, and severe fatigue on six (11%) of the trials. In a third study (15), two of 10 subjects dropped out because they had headaches on decaffeinated-coffee days that were severe enough to prohibit productive work at the subjects' jobs. In a fourth study of subjects taking 100 mg/day of caffeine in capsules (42), headache and fatigue occurred even upon deprivation of this low dose. In fact, "the headache, lethargy and nausea experienced after placebo substitution in six of the seven subjects were incompatible with normal functioning; subjects occasionally reported going to bed early with flu-like symptoms and two subjects reported vomiting. We judge the peak level of disruption encountered by six of the seven subjects to be clinically significant" (27).

*Prevalence of withdrawal symptoms.* Among retrospective surveys, an early study (43) found that 8%–9% of 239 housewives who drank coffee reported headaches after cessation, and 38% stated that they would feel "half-awake" if they stopped coffee use. Among headache patients, 20% stated that lack of coffee would result in headaches (41). Among psychiatric inpatients, 20% reported headaches upon caffeine cessation (44). Such survey data may actually underestimate the prevalence of withdrawal symptoms, as many caffeine users may be unaware that intermittent drowsiness, headaches, and fatigue could be due to the absence of caffeine.

Among prospective studies, a study of postoperative headache found that the prevalence of headaches increased from 0% in nonusers of caffeine to 43%–46% in those who used 200–1,000 mg/day to 73% among those who used more than 1,000 mg/day (26). In three trials, among nonpatient (i.e., volunteer) moderate coffee drinkers (3–7 cups/day), the prospective prevalence of headaches was 23%–56%; of drowsiness, 38%; and of fatigue, 38% (15, 24, 45). The prospective prevalence of caffeine withdrawal headaches following cessation of heavy caffeine use (more than 600 mg/day) in patient samples has been reported to be between 82% and 100% (41, 46).

*Withdrawal symptoms and self-administration of caffeine.* In three studies (15, 22, 24), subjects who had withdrawal headaches, drowsiness, or fatigue upon placebo substitution were subsequently more likely to self-administer caffeinated coffee in preference to decaffeinated coffee than were subjects who did not experience these withdrawal symptoms. In two studies (15, 24), the occurrence of withdrawal effects was followed by self-administration more than 80% of the time; however, on 30%–40% of occasions, self-administration occurred in the absence of withdrawal symptoms. Thus, the presence of withdrawal symptoms is highly predictive of caffeine self-administration, but the absence of withdrawal symptoms does not predict the absence of caffeine self-administration.

### *Conclusions With Respect to Caffeine Withdrawal*

At the present time, there appears to be sufficient evidence to justify inclusion of a caffeine withdrawal syndrome in *DSM-IV* and *ICD-10*, with headache, decreased arousal, and fatigue listed as the valid symptoms. These symptoms have been shown to be due to the specific deprivation of caffeine, they have a characteristic time-limited course, they can occur at moderate caffeine intakes, they can occur in a substantial proportion of coffee drinkers, and they appear to contribute to the self-administration of caffeine. Finally, the earlier rationale for not including caffeine withdrawal—i.e., the symptoms are not severe—appears not to be true. Experimental tests of tolerance to the behavioral effects of caffeine and further study of the association of tolerance and withdrawal symptoms, the biochemical mechanisms of withdrawal symptoms, and the prevalence of symptoms of caffeine withdrawal are needed.

### *Inclusion of the Caffeine Withdrawal Syndrome and the Goals of* DSM

*Clinical usefulness for making treatment and management decisions.* Heavy caffeine use appears to be quite prevalent among psychiatric patients (3–5) and alcohol and drug abusers (47, 48). Many psychiatric, alcohol/drug abuse, and medical inpatient units prohibit caffeinated coffee; thus, some patients may be forced into a caffeine withdrawal syndrome when entering these units. This could interfere with the diagnosis and treatment of such patients, since the symptoms of caffeine withdrawal (headache, fatigue, and drowsiness) could mimic or falsely exaggerate symptoms of anxiety, depression, dementia, delirium, stimulant withdrawal, or drug-induced sedation. Having a diagnosis of caffeine withdrawal syndrome would sensitize clinicians to this possibility.

Prevalence is a consideration for clinical usefulness. On the basis of the data described earlier, a conservative estimate of the prevalence of caffeine withdrawal symptoms is that 5% of caffeine users develop headache, drowsiness, or fatigue upon cessation. Even such a low prevalence is important, given that 85%–90% of U.S. adults use caffeine daily.

*Acceptability to clinicians and researchers.* Clinicians and scientists may welcome the inclusion of a caffeine withdrawal syndrome, since other stimulants (e.g., amphetamine and cocaine) have accepted withdrawal syndromes but caffeine does not. Opposition to inclusion of a caffeine withdrawal syndrome might come from those who believe that it is less severe than other withdrawal syndromes. We are unaware of survey or experimental comparisons of caffeine with other withdrawal syndromes. However, the data we have cited suggest that symptoms of caffeine withdrawal can be severe and can interfere with role functioning. In addition, the data suggest that the presence of caffeine withdrawal symptoms contributes to the continued use of caffeinated beverages.

Opposition to including a caffeine withdrawal syndrome might also be due to a fear that its acceptance implies acceptance of caffeine as a drug of dependence. In recent years, many drugs that are not drugs of dependence have been identified as producing withdrawal symptoms upon cessation (e.g., antidepressants and antipsychotics) (49, 50). Thus, accepting that withdrawal of a drug can produce symptoms no longer necessarily implies accepting that it is a drug of dependence.

## CAFFEINE ABUSE

### *Basic Science Criteria*

The *DSM-III-R* criteria for psychoactive substance abuse are "continued use . . . despite knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the substance" and "recurrent use of the substance in situations when use is physically hazardous (e.g., driving while intoxicated)" (p. 169). A working draft of *ICD-10* defines harmful use as "a pattern of use which is causing damage to health. The damage may be physical or mental." Two basic science areas relevant to abuse are caffeine psychoactivity and harmful medical effects.

*Psychoactive effects of caffeine.* Basic science definitions of psychoactivity usually refer to the ability to discriminate between a drug and placebo on the basis of the drug's CNS effects. Nonhuman subjects readily discriminate caffeine from placebo and respond as if caffeine has weak amphetamine-like effects (51–54). Humans also readily discriminate caffeine, even at very low doses (e.g., 10–56 mg) (42, 55).

In studies of self-reported effects, single doses (100–400 mg) of caffeine produce slight increases in elation, positive mood, and amphetamine-like effects (39, 55–60). These effects are generally less consistent and of a smaller magnitude than those seen with amphetamine. In addition, at these same doses, caffeine often produces several presumably aversive effects (e.g., increased anxiety and dysphoria) (61, 62).

*Harmful effects of caffeine.* Reviews vary widely in their conclusions about whether caffeine can cause physical disorders (8, 63). However, the *DSM-III-R* criteria for abuse include the ability of a drug not only to initiate a new disorder but also to aggravate an existing disorder. With respect to the latter category, a recent survey (64) indicated that more than 75% of physician specialists recommended cessation of caffeine for patients with several common disorders: anxiety, arrhythmias, esophagitis, fibrocystic disease, insomnia, palpitations, and tachycardia.

Behavioral disorders resulting from caffeine use are well recognized. As indicated in *DSM-III-R* (p. 139), caffeine use of even as little as 250 mg/day can cause restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought or speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation.

### *Clinical Criteria*

Clinical indications for drug abuse include use despite problems from a drug, hazardous use, and unsanctioned (i.e., socially disapproved) use (10, 12).

*Use despite problems.* Case reports describe substance abusers (65) and anorexic patients (66) who have persistent, very high caffeine intakes with resultant symptoms of intoxication. In some cultures, caffeine capsules are abused and have been linked to psychoses and anxiety disorders (67). On the other hand, whether patients persist in the use of caffeine despite physicians' recommendations has not been reported.

*Hazardous use.* Since caffeine intoxication can produce restlessness, excitement, muscle twitches, rambling flow of thought, and psychomotor agitation, it is possible that these consequences could impair driving, working with machinery, etc. However, case reports of such events have not been published.

*Unsanctioned use.* A urine screen survey found very high blood levels of caffeine (more than 12.5 mg/ml) in 5% of competitive bicyclists (68). A study of cocaine samples found that caffeine was a common adulterant (69).

### *Summary of Caffeine Abuse Study Results*

Caffeine can produce positive mood and amphetamine-like effects, but these appear to be less robust than those associated with prototypic drugs of abuse. Case reports indicate instances of repeated caffeine intoxication; however, the prevalence of such phenomena is unclear. Persistent use of caffeine in the face of a known illness aggravated by caffeine has not been documented, nor have caffeine-induced accidents been documented.

## CAFFEINE DEPENDENCE

### *Basic Science Criteria*

Demonstration that a drug serves as a reinforcer is thought to be crucial to definitions of drug dependence (70). Reinforcing effects are inferred when subjects consistently self-administer a drug at a rate greater than or in preference to placebo.

In nonhuman subjects—even those previously trained to self-administer opioids, cocaine, etc.—caffeine either does not serve as a reinforcer or does so marginally or inconsistently (71). Two early studies (72, 73) suggested that in humans, caffeine in coffee can serve as a reinforcer, but these studies lacked adequate controls (i.e., decaffeinated coffee or return-to-baseline conditions). A third study (60) used preference for ingesting caffeine capsules over placebo capsules to infer reinforcing effects among light users of caffeine and found no preference for 100-mg or 300-mg caffeinated capsules. A fourth study (74) compared the rate of self-administration of decaffeinated coffee to that of coffee with 25, 50, 100, 200, and 400 mg of caffeine added and found slight increases in administration of the 50-mg and 100-mg doses.

In three well-controlled studies by Griffiths et al. (22, 45, 75), a subset of subjects consistently self-administered caffeinated coffee or capsules rather than placebo during double-blind tests. Four studies by our group (24, 76–78) replicated these effects and extended them to low doses (25–50 mg). In several of these studies, caffeine self-administration was maintained under double-blind conditions across many independent tests (e.g., 12–26 tests) for long periods of time (e.g., 6 months). Although these results were quite robust in some individuals, reasons for individual differences in reinforcing effects have not been established (45, 76, 77).

The magnitude of reinforcing effects from caffeine can be estimated by noting how hard human beings will work to obtain caffeine. In one study (75), the amount of work required in order to obtain caffeinated coffee, decaffeinated coffee, caffeine capsules, or placebo capsules was increased over time. Self-administration of placebo capsules dropped off quickly, self-administration of caffeinated coffee persisted the longest, and decaffeinated coffee and caffeine capsules were self-administered at an intermediate level. In another study (79), increasing the amount of work required to obtain coffee decreased coffee consumption to an extent similar to that obtained with cigarettes. In that study, subjects made up to 2,500 lever pulls for 2-oz servings of caffeinated coffee.

### *Clinical Criteria*

The *DSM-III-R* and *ICD-10* dependence criteria of withdrawal symptoms, tolerance, use to avoid withdrawal symptoms, use despite knowledge of harm, and hazardous use have already been discussed. We now discuss the five other clinical criteria in *DSM-III-R* or *ICD-10.*

*Loss of control.* This criterion is operationalized in *DSM-III-R* as "substance often taken in larger amounts or over a longer period than the person intended" (p. 167) or "persistent desire or one or more unsuccessful efforts to cut down or control substance use" (p. 168).

There are no reports of whether some caffeine users would describe themselves as losing control of their caffeine intake. Some case reports and clinical reviews suggest that there are some patients who wish to quit caffeine but are unable to do so and that relapse rates are high (44, 80). However, neither prospective studies of attempts to stop using caffeine nor survey data on the prevalence of attempts to stop using caffeine and their success rates are available. Nor are there any data on the difficulty that caffeinated coffee users have with switching to decaffeinated coffee.

*Time with drug.* This criterion is defined in *DSM-III-R* as "a great deal of time spent in activities necessary to get the substance . . . , taking the substance . . . , or recovering from its effects" (p. 168). Application of this criterion to readily available licit drugs is problematic. Although caffeinated beverages can be quickly made, in some historical periods and in some present cultures, preparation and consumption of coffee/tea have been described as time-consuming (8). To our knowledge, instances of spending a great deal of time on preparation and use of beverages containing caffeine have not been reported in the recent Western literature.

*Progressive neglect.* This criterion is defined in *DSM-III-R* as "important social, occupational, or recreational activities given up or reduced because of substance use" (p. 168). Again, this criterion is not readily applicable, as caffeine is widely available, can be used in social situations, and produces no aftereffects. Instances of progressive neglect due to caffeine use have not been reported.

*Narrowing of the repertoire.* This criterion is defined in a draft of *ICD-10* as "a narrowing of the personal repertoire of patterns of use." The construct is not included in *DSM-III-R.* Caffeine users do appear to have very regular patterns of use (74); however, the narrowing-of-repertoire criterion implies resistance to changes in the pattern of drug intake. Although this has not been tested, most coffee drinkers appear to be flexible with respect to environmentally induced changes in the timing of their caffeine intake, perhaps because caffeine is available in almost all settings.

*Rapid reinstatement.* Rapid reinstatement is defined in the *ICD-10* draft as "evidence that return to use after a period of abstinence leads to more rapid reinstatement of other features of the syndrome than occurs with nondependent individuals." This construct is also not included in *DSM-III-R.* At present there are no studies of cessation of caffeine and relapse back to caffeine use; thus, no data on this construct are available.

### *Construct Validity of the Dependence Syndrome*

One important indication of the validity of a disorder is the presence of familial patterns or biological markers. Several studies (81–86) have noted higher concordance rates of coffee use among monozygotic twins than among dizygotic twins. Heritability coefficients were quite similar across most studies: 0.46–0.49. It is important to note that these studies examined coffee use—not abuse, dependence, or withdrawal. Thus, a genetic propensity to use caffeine has been suggested, not a propensity to become dependent.

Other studies have noted a higher concordance among monozygotic twins for tolerance to sleep disruption from coffee (87). Another piece of genetic evidence is that taste sensitivity to caffeine is under strong control of genotype (88). Finally, although this is not direct evidence, variations in metabolism of caffeine across users and nonusers occur (89), and persons with faster clearance appear to be more tolerant to the sleep disruption from coffee (90). However, an earlier study did not find this (39).

### *Summary of Caffeine Dependence Study Results*

Although caffeine has not been shown to be a reliable reinforcer in nonhuman subjects, in human beings caffeine serves as a very reliable reinforcer for some individuals. Analyses of the strength of caffeine's reinforcing effects have just begun; thus, it is not possible to conclude whether, in some individuals, caffeine is as strong a reinforcer as nicotine, alcohol, etc. As indicated earlier, the evidence for withdrawal symptoms and for behavioral harm from caffeine is robust. The evidence for tolerance and physical harm is suggestive. In contrast to these positive results from basic science studies, clinical data on traditional indicators of dependence are clearly lacking.

## CAFFEINE ABUSE AND DEPENDENCE

### *Conclusions With Respect to Caffeine Abuse and Dependence*

At the present time there is insufficient evidence to include caffeine abuse or dependence in *DSM-IV*. This conclusion is based mainly on the notion that a new disorder should not be included in *DSM* or *ICD* until there is a substantial and compelling database. This is especially important with disorders that could be applied to large numbers of individuals. At present a substantial basic research database exists for caffeine dependence (i.e., caffeine can serve as a reinforcer, produce withdrawal, and cause behavioral harm), but a clinical database is almost completely absent. The type of clinical data that would be necessary for adding caffeine dependence include empirical evidence that a substantial proportion of coffee drinkers 1) try to stop and cannot, 2) have difficulty switching to decaffeinated coffee, and 3) use caffeine despite knowledge that they have health problems which are aggravated by caffeine. Other data of interest would be 4) heavy coffee drinkers' ratings of the difficulty of stopping caffeine intake compared to stopping cigarette smoking or drinking alcohol, 5) whether tolerance to important behavioral effects (e.g., relief of fatigue) occurs, 6) whether coffee use escalates over time, 7) how often coffee is used to avoid withdrawal symptoms, and 8) what the prevalence of caffeine dependence is.

### *Exclusion of Caffeine Abuse and Dependence and the Goals of* DSM

*Clinical usefulness for making treatment and management decisions.* Although we have not recommended the inclusion of the diagnoses of caffeine abuse and dependence, some persons might state that their inclusion is needed in order to be consistent with the recent emphasis in medical "wellness" and drug-free alcohol/substance abuse programs on complete abstinence from all drugs. In addition, there is some evidence that caffeine use promotes alcohol use and abuse (8, 47, 91). In a similar vein, inclusion would be consistent with treatment programs that emphasize organismic rather than drug factors in the genesis and maintenance of alcohol/drug abuse. In addition, caffeine intake is quite high in some subcultures (8); thus, caffeine dependence might actually be relevant in these settings. Finally, and perhaps most importantly, one could argue that inclusion of caffeine abuse would promote identification of patients who repeatedly experience intoxication and would suggest that in addition to treatment for caffeine intoxication, such patients need acute treatment for an abuse/dependence problem.

On the other hand, one clinical reason not to include caffeine abuse and dependence is that caffeine intoxication is already included in *DSM-III-R* and that such a diagnosis should remind psychiatrists that excessive caffeine use can mimic several psychiatric conditions, including anxiety disorders and drug withdrawal. A second clinical reason for not including caffeine abuse and dependence is that, at present, only a few treatments for caffeine abuse and dependence have been tested (92, 93). Whether treatments used for other drugs (e.g., 12-step programs, behavioral therapy, pharmacological replacement) would be efficacious is debatable. Thus, the therapeutic benefits of a diagnosis of caffeine abuse or dependence are not clear.

Finally, at present patients with symptoms of caffeine dependence can be given the *DSM-III-R* diagnosis of psychoactive substance dependence not otherwise specified. This residual category is for disorders that occur infrequently. Thus, a determination of the prevalence of caffeine dependence phenomena both in treatment settings and in the general population would be helpful in deciding whether a new disorder should be created or whether instances of caffeine dependence are so infrequent that they should continue to be put in this residual category.

*Acceptability to clinicians and researchers.* A decision to exclude caffeine abuse and dependence could provoke negative comments from primary care physicians, psychiatrists, and substance abuse clinicians who have patients who recognize that caffeine is aggravating their disorders, who have severe headaches upon cessation of caffeine, or who are unable to stop caffeine use. Such clinicians might accuse *DSM-IV* of being inconsistent in its handling of various drug use problems or of being politically cowardly.

A decision to include caffeine abuse and dependence may provoke negative comments from coffee manufacturers, the general public, and some substance abuse clinicians. Coffee manufacturers will obviously fear a public debate like that which occurred with respect to tobacco. The general public and some substance abuse clinicians will state that inclusion of caffeine dependence trivializes other more damaging substance use disorders, promotes the view of *DSM* as a tool for psychiatrists to aggrandize diagnostic territory, and undermines the credibility of APA. These groups will focus on the lack of clinical information on caffeine abuse and dependence and the absence of studies comparing the relative strengths of caffeine dependency versus alcohol, nicotine, and other dependencies.

## FINAL COMMENT

Whether caffeine withdrawal, caffeine abuse, or caffeine dependence should be added to the *DSM* or *ICD-10* classifications will be a controversial topic. This article was written in the belief that empirical data and established criteria for acceptance of disorders are better guides for such a decision than a priori beliefs or philosophical positions.

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# Attempted Suicide Among Young Adults: Progress Toward a Meaningful Estimate of Prevalence

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*Objective: The results of epidemiologic surveys on attempted suicide are often difficult to interpret; they compare and provide varying estimates of the prevalence of attempted suicide. The authors sought to estimate the prevalence of attempted suicide in a young adult population and to define more precisely what respondents mean when they report a suicide attempt. Method: Survey respondents were a representative sample of all 18–24-year-old freshman students at a major public university. The self-administered, anonymous survey included questions about suicidal thoughts and behaviors and about any injury and need for medical care resulting from reported attempts. Results: Of the 694 respondents, 374 (54%) reported having ever considered suicide and 181 (26%) had considered suicide during the preceding 12 months. Thirteen (2%) students reported having attempted suicide during the preceding 12 months, and 72 (10%) reported ever having attempted suicide. The number of students answering affirmatively to questions about injuries sustained, medical care sought, and hospitalization as a result of attempted suicide decreased progressively: only 18 (3%) students reported having ever sought medical care due to a suicide attempt, and seven (1%) were ever hospitalized. Conclusions: The prevalence of self-reported attempted suicide is not representative of the prevalence of self-injury and provides little information concerning the seriousness of the attempt. The use of specific questions similar to those used in this study should be considered in future surveys.*

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Attempted suicide is not only a major risk factor for subsequent completed suicide (1, 2) but also a morbid health event that results in personal suffering and considerable economic cost (3). Epidemiologic surveys provide useful information about the magnitude of the problem of attempted suicide in the general population and among specific populations such as students.

Although previous surveys have varied considerably in methodology and in the questions asked, some estimates of the prevalence of self-reported attempted suicide are available. The National Adolescent Student Health Survey (4), a survey of a national probability sample of eighth- and tenth-grade students, yielded an estimated lifetime prevalence of attempted suicide among high school students of about 14%. One population-based study, the Epidemiologic Catchment Area (ECA) study (5), which involved five geographic areas, found a lifetime prevalence of attempted suicide among all adults of 2.9% and a prevalence among 18–24-year-olds of 3.4%. Several surveys of specific college student

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populations have been done (6–9); these provide estimated lifetime prevalences of self-reported attempted suicide as high as 15%.

There is a spectrum of suicidal thoughts and behaviors that begins with ephemeral thoughts about suicide and proceeds to attempted suicide without injury, to attempted suicide with serious injury, and finally to completed suicide. Results of surveys designed to estimate the incidence or prevalence of suicidal thoughts (ideation) and suicidal behaviors are often difficult to interpret and compare because they simply ask, "Have you attempted suicide?" Rarely is an attempt made to elucidate the seriousness of suicidal intent or to ascertain what respondents mean by "suicide attempt" in terms of the severity of the outcome. This problem is exemplified by the paradoxically higher estimated lifetime prevalence of attempted suicide for younger respondents than for older respondents, as in the ECA study (5). It is possible that some thoughts or behaviors reported as attempted suicide by younger respondents are not reported as such by older respondents.

Possible approaches to clarifying what respondents mean when they report having attempted suicide include specifically defining the term "suicide attempt" for the respondents, using more precise terminology when asking about attempted suicide, and specifying the outcome of the attempted suicide through a series of increasingly specific questions. In the present study, we employed the latter two approaches in a survey addressing suicidal thoughts and behavior among college students. To define attempted suicide for the respondents, we asked specifically whether the respondents had "attempted to take their own lives" rather than whether they had "attempted suicide." We also asked a series of increasingly specific questions about the outcomes of reported attempts, in terms of injury, medical care received, and hospitalization. By asking more precise questions about attempted suicide and by allowing respondents to clarify what they meant by "suicide attempt" in terms of injury outcome and medical care received, we tried to get more interpretable estimates of the prevalence of suicidal behaviors.

## METHOD

We surveyed a representative sample of students from a single public university in Nevada to determine the annual and lifetime prevalence of suicidal ideation and attempted suicide among the respondents. During the week in which the survey was administered, there were 61 freshman English classes, with 1,218 students enrolled at the beginning of the semester. Each instructor of freshman English was asked to have his or her class participate. Students were not told about the survey until the day it was administered. The instructors of seven classes chose not to invite their students to participate for a variety of reasons, none of which had to do with recent suicides or suicide attempts. Of the 804 students present on the day of the survey in the remaining 54 classes, 774 (96%) completed forms. This represented 64% of the enrolled freshmen. Since the survey was anonymous, we were not able to obtain demographic or other information for the students who were not in class on the day the survey was administered.

The survey was administered during regular class periods in a single week. Before distributing the questionnaires, the instructor in each class read a brief, standardized introduction indicating that the survey was voluntary and anonymous. Participants were then given a self-administered questionnaire that included written instructions and enough information about the study to enable them to make an informed decision regarding their participation in it. Students were told that the survey was a joint project of state and federal public health agencies. No personal identifiers were put on the questionnaires. The respondents were asked to return the questionnaires (completed or blank) in an envelope that was provided.

The survey instrument included a set of demographic items, questions about the respondent's history of suicidal thoughts and behaviors, and a series of questions intended to examine certain potential risk factors for attempted suicide. The present analysis is limited to data on the respondents' histories of suicidal thoughts and behaviors. The questions about suicidal ideation and attempted suicide are listed in appendix 1.

Lifetime and annual prevalences of specific suicidal thoughts, behaviors, and outcomes were calculated for the 694 respondents who were 18–24 years of age. Outcomes in terms of injury and medical care received were assumed to apply to the most recent attempted suicide. This may have resulted in a slight overestimation of the annual prevalence of injury and medical care received because of attempted suicide because, in a few cases, there were not only attempts in the preceding 12 months but also more remote attempts. Statistical significance testing was done by using the two-tailed Fisher exact test or the Mantel-Haenszel chi-square.

## RESULTS

Lifetime prevalences of suicidal thoughts and behaviors are presented in table 1. In response to the question, "Have you EVER had thoughts of taking your life, even if you would not really do it?" 53.9% of the respondents answered affirmatively. Somewhat fewer respondents reported having ever thought of a specific way of taking their own lives, and the lifetime prevalence of actual attempted suicide was 10.4%. The proportion of respondents who reported ever suffering injury or illness as a result of attempting suicide was 4.6%, but the proportion who reported seeking medical care as a result of a attempted suicide was 2.6%. Only 1.0% of the respondents reported an overnight hospitalization after attempted suicide.

Of the 72 respondents who reported ever having attempted suicide, 44% actually suffered an injury, 25% sought medical care, and 10% were admitted to the

**TABLE 1. Lifetime and 12-Month Prevalences of Suicidal Ideation and Attempted Suicide Among 694 College Freshmen**

| | Men (N=320) | | Women (N=374) | | Total (N=694) | |
|---|---|---|---|---|---|---|
| Suicidal Ideation or Attempted Suicide | N | % | N | % | N | % |
| Thoughts of taking own life | | | | | | |
| Ever[a] | 142 | 44.4 | 232 | 62.0 | 374 | 53.9 |
| During preceding 12 months | 78 | 24.4 | 100 | 26.7 | 178 | 25.6 |
| Thoughts of specific ways of taking own life | | | | | | |
| Ever | 139 | 43.4 | 183 | 48.9 | 332 | 47.8 |
| During preceding 12 months | 62 | 19.4 | 59 | 15.8 | 121 | 17.4 |
| Attempted to take own life | | | | | | |
| Ever[b] | 15 | 4.7 | 57 | 15.2 | 72 | 10.4 |
| During preceding 12 months[c] | 2 | 0.6 | 11 | 2.9 | 13 | 1.9 |
| Suffered injury or illness as a result of suicide attempt | | | | | | |
| Ever[d] | 7 | 2.2 | 25 | 6.7 | 32 | 4.6 |
| During preceding 12 months | 1 | 0.3 | 6 | 1.6 | 7 | 1.0 |
| Sought medical care as a result of suicide attempt | | | | | | |
| Ever[e] | 4 | 1.3 | 14 | 3.7 | 18 | 2.6 |
| During preceding 12 months | 0 | 0.0 | 3 | 0.8 | 3 | 0.4 |
| Admitted to a hospital as a result of suicide attempt | | | | | | |
| Ever | 2 | 0.6 | 5 | 1.3 | 7 | 1.0 |
| During preceding 12 months | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

[a] Significant difference between men and women (Mantel-Haenszel $\chi^2$=21.6, df=2, p=3×$10^{-6}$).
[b] Significant difference between men and women (Mantel-Haenszel $\chi^2$=20.6, df=2, p=6×$10^{-6}$).
[c] Significant difference between men and women (p=0.04, Fisher's exact test, two-tailed).
[d] Significant difference between men and women (Mantel-Haenszel $\chi^2$=7.9, df=2, p=0.005).
[e] Significant difference between men and women (Mantel-Haenszel $\chi^2$=4.2, df=2, p=0.04).

hospital. Thoughts of suicide, attempted suicide, attempted suicide with injury, and attempted suicide resulting in the use of medical care were all significantly more common among women (table 1).

Similar patterns were seen for the prevalence of suicidal thoughts and behaviors during the 12 months preceding the survey (table 1). The prevalence of attempted suicide was much lower than the prevalence of suicidal ideation. Suicide attempts reported to have occurred in the 12 months preceding the survey resulted in injury approximately half the time, rarely resulted in the use of medical care, and in no case caused overnight hospitalization. Attempted suicide in the 12 months preceding the survey was also more common among women than men.

## DISCUSSION

We found that the prevalence of self-reported attempted suicide in this study did not reflect the prevalence of self-injury due to a suicide attempt. Moreover, had we not extended our series of questions beyond simply inquiring about past history of attempted suicide, we would have learned nothing about what the respondents meant in terms of the seriousness of the attempt. In fact, we found a cascade of decreasing prevalence as the severity of outcome increased in terms of injury and need for medical attention.

These findings merit emphasis because they profoundly affect the way we should interpret results of the many surveys that have been done to estimate the prevalence of attempted suicide. The high prevalence of self-reported attempted suicide among certain population groups, such as adolescents, correctly highlights the magnitude of this public health problem.

Our results indicate, however, that the nature of the problem is not one of large numbers of injured people, although this may be the impression generated by reports of a lifetime prevalence of attempted suicide among young adults of up to 15% (7). The high prevalence of attempted suicide is a serious problem because it reflects a considerable amount of psychological suffering and desperation for most suicide attempters and because suicide attempters are at high risk of later completed suicide (1, 2).

We found a disparity between the proportion of respondents who reported having attempted suicide and the proportion who suffered an injury or sought medical care as a result of the suicide attempt despite our having asked very specifically about an attempt on one's life rather than simply asking about "suicide attempts." This should be considered when designing future surveys. To obtain information about suicide attempts that actually involve self-harm, a series of questions similar to the ones used in this survey may be necessary.

Rarely have past surveys on attempted suicide addressed the methodological problem of defining what is meant by respondents when they report having attempted suicide. To ascertain the lethality of the respondent's intent, one community survey (10) asked the questions, "Have you ever deliberately harmed yourself, but in a way that stopped short of a real intent to take your life?" and "Have you ever made an intentional attempt to take your life?" Another cross-sectional study of a relatively small, nonrandom sample of high school students found a disparity similar to that found in our study between the frequency of reported attempted suicide and use of medical care as a result of the attempt (11).

Our estimated prevalences of suicidal ideation and attempted suicide are comparable to the highest estimates that have been found in other studies of attempted suicides among young adults. The finding that women have a higher prevalence of attempted suicide than men is consistent with findings from past studies of attempted suicide (5, 12).

Since participation in this survey was anonymous, we could not contact students who were absent on the day of the survey or students who had dropped English earlier in the semester. This limitation may result in a bias in our estimation of prevalences of suicidal thoughts and behaviors, but the direction of this potential bias is not known. Also, we could not compare the demographic characteristics of the study participants with those of students who were not in class on the day of the survey. Our 96% response rate among the freshman students who attended class on the day of the survey, however, suggests that this survey is highly representative of this group.

Another limitation that this survey shares with other confidential surveys (13) is that the responses could not be externally validated. Future studies are needed to establish the validity of self-reported suicidal behaviors in general. If specific and quantifiable outcomes (such as those used in our study) are found to be valid, they could be used to provide meaningful surveillance data through periodic surveys.

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## APPENDIX 1. Questions About Suicidal Ideation and Attempted Suicide

### *Suicidal Ideation*

Have you EVER had thoughts of taking your life, even if you would not really do it?

During the PAST 12 MONTHS have you had such thoughts?

Have you EVER thought about specific ways to take your life even if you would not really do it?

During the PAST 12 MONTHS have you thought about specific ways that you could take your own life?

### *Attempted Suicide*

Have you EVER made an attempt to take your own life?

During the PAST 12 MONTHS have you made an attempt to take your own life?

If "yes" to one of above:

Have you suffered an injury or illness as a result of trying to take your own life?

Did you go to a doctor, emergency room, or other health facility for the resulting injury or illness?

Were you admitted to a hospital to stay overnight or longer as a result of trying to take your own life?

# The Relationship Between Adolescent Suicidal Behavior and Life Events in Childhood and Adolescence

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Objective: *Although the relationship between experience of problematic life events and adolescent suicidal behavior has frequently been recognized during the past decade, few studies of life events have been initiated that discriminated between adolescent suicide attempters and depressed adolescents. Therefore, the authors compared adolescent suicide attempters with both depressed and nondepressed adolescents who never attempted suicide with respect to life events that happened in two periods: childhood (defined as the period up to age 12 years) and adolescence (age 12 and older).* Method: *Using a semistructured interview, the authors gathered life event data about childhood and adolescence from three groups of adolescents: 48 suicide attempters, 66 depressed adolescents who had never made a suicide attempt, and 43 nondepressed adolescents who had never made a suicide attempt.* Results: *The group of adolescents who attempted suicide differed from both of the other groups in that they had experienced more turmoil in their families, starting in childhood and not stabilizing during adolescence. During adolescence, they were more often sexually abused. During the last year before the attempt, further social instability, such as changes in residence and having to repeat a class, occurred.* Conclusions: *For suicidal adolescents, the suicide attempt seems embedded not just in the problems every adolescent has to deal with but in greater turmoil in their families, rooted in childhood and not stabilizing during adolescence, in combination with traumatic events during adolescence and social instability in the year preceding the attempt.*

(Am J Psychiatry 1992; 149:45–51)

In their impressive review of attempted suicide in adolescence, Spirito et al. (1) stated, "Presence of stressful life events . . . seems to have important implications for understanding suicide attempts in children and adolescents." Nevertheless, although the relationship between experience of problematic life events and adolescent suicidal behavior has frequently been recognized during the past decade (2, 3), few studies of life events have been initiated that discriminated between adolescent suicide attempters and depressed adolescents. This comparison is essential because many life events that take place in the lives of suicide attempters are also found in the lives of adolescents who report depressed mood (4), which implies that not taking depression into account is problematic when identifying life events specific for adolescent suicide attempters.

Several studies compared suicidal adolescents with heterogeneous psychiatric groups of nonsuicidal adolescents (5–7) or with other clinical groups (8, 9). However, it is not clear from these studies whether the compared groups were depressed or not.

Two studies (10, 11), however, made comparisons using depressed groups. Friedman et al. (10) compared suicidal depressed adolescents with nonsuicidal depressed adolescents but restricted their research to family history of illness. Chronic psychiatric illness of a parent (especially depression) was more frequently found among suicide attempters. Cohen-Sandler et al. (11) compared suicidal children and young adolescents (5–14 years old) with depressed and other psychiatric control groups regarding life events during different developmental periods. They found that more life events were related to suicidal behavior with increasing age.

If the results of Cohen-Sandler et al. were also applicable to adolescents, they would agree with those of

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Jacobs (12), who compared 50 adolescent suicide attempters with matched control subjects from schools. He hypothesized that 1) the first of four phases leading to a suicide attempt consists of a longstanding history of problems from childhood to the onset of adolescence and 2) the second phase is a period of "escalation of problems" at the onset of adolescence in excess of those "normally" associated with adolescence (p. 64).

In our opinion, Jacobs failed to find adequate support for his valuable hypotheses because his data analysis was rather obscure and because, by comparing suicidal adolescents with normal adolescents, he did not account for depression. A comparison of suicide attempters with both depressed and "normal" adolescents (as a baseline for "normal" adolescent turmoil) may give more solid information about his hypotheses.

In addition, analysis of Jacobs' hypotheses requires the specification of the period (childhood or adolescence) during which life events have taken place. Therefore, the present study compared adolescent suicide attempters with both depressed and nondepressed adolescents who never attempted suicide with respect to life events that happened in two periods: childhood (defined as the period up to age 12) and adolescence (age 12 and older). Moreover, because of the growing evidence about the importance of recent life events regarding suicide attempts and psychiatric disorder in young people (11, 13, 14), the last year before the attempt (for the suicide attempters) or before the interview (for the other groups) was studied separately.

## METHOD

### *Subjects*

Three groups of subjects were asked to cooperate with this study. The first group comprised 41 girls and seven boys 14–21 years old (mean±SD age=17.5±1.5 years) who attempted suicide 1–52 weeks before the measurement date. The second group consisted of 52 girls and 14 boys 14–21 years old (mean=17.9±1.6) who suffered from a depressed mood at the time of assessment and had never attempted suicide. (For reasons of readability, the adolescents who suffered from a depressed mood will be referred to as "depressed adolescents" in the remainder of the text.) The third group comprised 31 girls and 12 boys 14–21 years old (mean=17.5±1.3), randomly selected from a "normal" school population. The three groups were not matched, but there were no significant differences among them in relevant sociodemographic features such as age (F=1.45, df=2, 154, p=0.24), sex ($\chi^2$=2.43, df=2, p=0.30), and current type of school ($\chi^2$=7.22, df=6, p=0.12).

Two methods were used to recruit subjects for this study. First, institutions for mental health care were asked for referrals, and, second, 9,393 secondary school students were screened (15). Approximately half of the suicide attempters and half of the depressed adolescents were recruited through the institutions of mental health care. The rest of the suicide attempters and depressed adolescents as well as the entire group of normal adolescents were recruited from among the 9,393 secondary school students. The suicide attempters and the depressed adolescents did not differ significantly in this recruitment procedure ($\chi^2$=3.1, df=2, p=0.08).

The study was performed in compliance with the U.S. Human Subject Research Guidelines. Informed consent was obtained from all subjects and their parents.

Almost two-thirds of the suicide attempters had taken an overdose of medicine or toxic substances, one-quarter had injured themselves, and the rest had thrown themselves in front of a moving vehicle, tried to hang themselves, or jumped from a height. The mean±SD score of the suicide attempters on the Suicide Intent Scale (16), 6.8±3.4, was comparable to that of 50 British adolescents who attempted suicide (2). Three suicide attempters had scores of 13, indicative of a strong suicide intent. The mean risk score of all 48 suicide attempters on the Risk-Rescue Rating (17) was 8.1±2.1, indicative of a moderately low risk, and their rescue score on this scale was 11.6±2.3, indicative of a moderately high rescue level.

The 66 depressed adolescents were tested for depression at two separate times. First, at the time of the screening procedure preceding the interview, they were selected randomly if they appeared to have a score of 46 or higher on the Zung Self-Rating Depression Scale (18) and had a score of at least 16 on the Depression Adjective Checklist (19). The depressed adolescents referred from the institutions of mental health care met Research Diagnostic Criteria (20) for major depressive disorder. The second assessment took place at the time of the interview. Subjects who had a score of 46 or higher on the Zung scale at that time were included in this study. Their mean score on the Zung scale was 51.9±5.2, compared with 49.4±11.7 for the suicide attempters and 33.5±5.6 for the normal subjects.

For the normal comparison group, 45 students were initially selected at random for interview from among the secondary school students screened. The criteria for selection were that these students reported they had never made a suicide attempt and that they did not score higher than 46 on the Zung scale or 16 on the Depression Adjective Checklist. Nevertheless, at the time of the interview, two students met the criteria for depression and were removed from the study, leaving 43 adolescents in the normal comparison group.

### *Measures and Data Analysis*

A semistructured interview including several self-report questionnaires was conducted with each subject by a graduate psychology student or a psychologist who was especially trained for this purpose. Before the actual data collection, a pilot study was carried out with eight adolescents; the interview was modified on the basis of the findings of this pilot study.

The Life Event Time Schedule, a part of the Life History Interview (4), was developed for this study. The

**TABLE 1. Number of Major Life Events Experienced During Childhood (up to 12 Years of Age) by Adolescents Who Attempted Suicide, Depressed Adolescents, and Normal Adolescents**

| | Suicide Attempters (N=48) | | Depressed Adolescents (N=66) | | Normal Adolescents (N=43) | | Kruskal-Wallis |
|---|---|---|---|---|---|---|---|
| Event | Mean | SD | Mean | SD | Mean | SD | H |
| Serious illness | 0.60 | 0.82 | 0.44 | 0.68 | 0.56 | 0.73 | 1.23 |
| Accident | 0.69 | 0.78 | 0.55 | 0.77 | 0.56 | 0.80 | 1.73 |
| Change in living situation | 0.38 | 0.84 | 0.30 | 0.80 | 0.12 | 0.45 | 4.19 |
| Change in caretaker | 0.48 | 0.85 | 0.21 | 0.54 | 0.16 | 0.43 | 5.62 |
| Separation of parents | 0.23 | 0.42 | 0.06 | 0.24 | 0.09 | 0.29 | 7.81[a] |
| Reunion of parents | 0.13 | 0.33 | 0.05 | 0.21 | 0.07 | 0.26 | 2.51 |
| Change of residence | 0.83 | 1.02 | 0.74 | 0.85 | 0.84 | 0.92 | 0.23 |
| Death of family member | 0.08 | 0.40 | 0.02 | 0.12 | 0.02 | 0.15 | 0.84 |
| Physical health event of family member | 1.19 | 1.39 | 0.89 | 0.99 | 1.23 | 1.66 | 0.46 |
| Mental health event of family member | 0.56 | 1.01 | 0.38 | 0.76 | 0.28 | 0.67 | 2.61 |
| Unemployment of family member | 0.25 | 0.48 | 0.11 | 0.31 | 0.07 | 0.26 | 5.83 |
| Imprisonment of family member | 0.06 | 0.24 | 0.01 | 0.12 | 0.00 | — | 4.03 |
| Sibling leaving home | 0.13 | 0.44 | 0.11 | 0.47 | 0.09 | 0.37 | 0.21 |
| Change of school or type of school | 0.71 | 0.92 | 0.77 | 0.84 | 0.65 | 0.72 | 0.63 |
| Repeating a class | 0.10 | 0.31 | 0.09 | 0.29 | 0.05 | 0.21 | 1.08 |
| Ending a relationship | 0.00 | — | 0.00 | — | 0.00 | — | 0.00 |
| Physical abuse | 0.19 | 0.49 | 0.14 | 0.43 | 0.00 | — | 6.29[b] |
| Sexual abuse | 0.17 | 0.48 | 0.05 | 0.21 | 0.05 | 0.21 | 3.34 |
| Criminal events | 0.04 | 0.29 | 0.12 | 0.41 | 0.19 | 0.55 | 4.12 |
| Total number of events | 6.81 | 3.91 | 5.03 | 3.68 | 5.02 | 3.11 | 8.00[c] |

[a] $p<0.05$; significant difference between suicide attempters and depressed adolescents (Tukey honestly significant difference procedure).

[b] $p<0.05$; significant difference between suicide attempters and normal adolescents (Tukey honestly significant difference procedure).

[c] $p<0.05$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

main objective of this instrument is to assess the occurrence of life events as well as when they took place. The Life Event Time Schedule consists of 77 items, chosen for their known importance regarding suicidal behavior. Nineteen of these items were examined for this study: serious illness, accident, change in living situation (for example, a change from living with one's biological family to living with a foster family), change in caretaker (for example, from two biological parents to one), separation of parents (parents living apart or divorced), reunion of parents, change of residence, death of a family member, events concerning the physical health of a family member (serious illness, hospital admission, becoming an invalid), events concerning the mental health of a family member (psychiatric hospital admission, nervous breakdown, contact with mental health institute), unemployment of a family member, imprisonment of a family member, sibling leaving home, change of school or type of school, repeating a class, ending a relationship, physical abuse, sexual abuse, and criminal events (breaking the law, prosecution, fine, or imprisonment). Because our primary interest lay in the occurrence of specific events, no effort was made to assign weights to the individual items.

The number of events reported was analyzed separately for three time periods—up to 12 years of age, from 12 years of age until the date of suicide attempt or the date of the interview, and the last year before the suicide attempt or date of interview. Univariate comparisons were made with the Kruskal-Wallis nonparametric analysis of variance (21). The distribution of the attained statistic, H, which was corrected for ties, is approximated by chi-square. To determine which groups were different from each other, a Tukey honestly significant difference procedure (22) was performed whenever H reached significance. In addition, for significant differences the percentage of subjects in each group who experienced the event in a given period is described in the text. This indicates the person-rate frequency of the events, as opposed to the event-rate data given in the tables.

## RESULTS

Table 1 shows the results for the period of childhood. These results indicate that suicide attempters differed from depressed adolescents in that they experienced more events of separation of their parents before the age of 12. This occurred in 11 (23%) of the suicide attempters, compared with four (6%) of the depressed adolescents and four (9%) of the normal adolescents. Suicide attempters also differed from normal adolescents in that they reported more events of physical abuse before the age of 12 than did normal adolescents. Seven (15%) of the suicide attempters, seven (11%) of the depressed adolescents, and none of the normal adolescents reported physical abuse in childhood. Besides these significant differences, suicide attempters experienced more problematic life events during childhood than did depressed and normal adolescents; this is indicated by the total number of events (table 1).

**TABLE 2. Number of Major Life Events Experienced During Adolescence (Age 12 and Later) by Adolescents Who Attempted Suicide, Depressed Adolescents, and Normal Adolescents**

| | Suicide Attempters (N=48) | | Depressed Adolescents (N=66) | | Normal Adolescents (N=43) | | Kruskal-Wallis |
|---|---|---|---|---|---|---|---|
| Event | Mean | SD | Mean | SD | Mean | SD | H |
| Serious illness | 0.27 | 0.49 | 0.44 | 0.70 | 0.30 | 0.64 | 2.15 |
| Accident | 0.73 | 1.14 | 0.41 | 0.70 | 0.28 | 0.55 | 3.67 |
| Change in living situation | 1.15 | 1.73 | 0.35 | 0.87 | 0.09 | 0.43 | 21.77[a] |
| Change in caretaker | 0.60 | 0.94 | 0.24 | 0.66 | 0.12 | 0.32 | 12.57[b] |
| Separation of parents | 0.31 | 0.55 | 0.11 | 0.31 | 0.05 | 0.21 | 10.82[b] |
| Reunion of parents | 0.31 | 0.69 | 0.21 | 0.62 | 0.14 | 0.41 | 2.79 |
| Change of residence | 0.38 | 0.76 | 0.30 | 0.61 | 0.33 | 0.61 | 0.09 |
| Death of family member | 0.06 | 0.32 | 0.09 | 0.29 | 0.09 | 0.37 | 0.94 |
| Physical health event of family member | 0.98 | 1.18 | 1.50 | 1.63 | 1.33 | 1.48 | 2.54 |
| Mental health event of family member | 1.29 | 1.79 | 1.12 | 1.20 | 0.70 | 0.99 | 3.81 |
| Unemployment of family member | 0.40 | 0.57 | 0.44 | 0.73 | 0.30 | 0.46 | 0.48 |
| Imprisonment of family member | 0.00 | — | 0.08 | 0.32 | 0.00 | — | 5.62 |
| Sibling leaving home | 0.48 | 0.82 | 0.39 | 0.76 | 0.63 | 0.95 | 1.89 |
| Change of school or type of school | 1.46 | 0.87 | 1.65 | 1.12 | 1.84 | 0.84 | 4.12 |
| Repeating a class | 0.33 | 0.52 | 0.32 | 0.53 | 0.21 | 0.47 | 1.97 |
| Ending a relationship | 0.90 | 0.78 | 0.91 | 1.02 | 0.81 | 0.91 | 0.58 |
| Physical abuse | 0.23 | 0.42 | 0.29 | 0.46 | 0.07 | 0.26 | 7.56[c] |
| Sexual abuse | 0.44 | 0.68 | 0.26 | 0.54 | 0.05 | 0.21 | 11.87[d] |
| Criminal events | 0.60 | 1.27 | 0.30 | 0.86 | 0.33 | 0.71 | 0.99 |
| Total number of events | 10.92 | 5.41 | 9.41 | 4.15 | 7.65 | 3.65 | 9.47[d] |

[a] $p<0.001$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

[b] $p<0.01$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

[c] $p<0.05$; significant difference between depressed and normal adolescents (Tukey honestly significant difference procedure).

[d] $p<0.01$; significant difference between suicide attempters and normal adolescents (Tukey honestly significant difference procedure).

There were more differences among the three groups from the age of 12 on (table 2). Suicide attempters differed from depressed and normal adolescents in that they experienced more changes in living situation and in caretaker as well as parental divorce or separation (of course, these variables are correlated). Twenty-one (44%) of the suicide attempters experienced changes in living situation, compared with 12 (18%) of the depressed adolescents and two (5%) of the normal adolescents. Eighteen (38%) of the suicide attempters reported changes in caretaker, compared with nine (14%) of the depressed adolescents and five (12%) of the normal adolescents. Thirteen (27%) of the suicide attempters experienced parental separation, compared with seven (11%) of the depressed adolescents and two (5%) of the normal adolescents. Suicide attempters differed from normal adolescents in that they reported more sexual abuse. Sixteen (33%) of the suicide attempters reported sexual abuse during adolescence, compared with 14 (21%) of the depressed adolescents and two (5%) of the normal adolescents. The suicide attempters reported a significantly higher number of total events than did normal adolescents (table 2).

Depressed adolescents reported more physical abuse during adolescence than did normal adolescents (table 2). Nineteen (29%) of the depressed adolescents reported physical abuse during adolescence, compared with 11 (23%) of the suicide attempters and three (7%) of the normal adolescents.

Table 3 shows the mean number of events reported by the subjects as happening in the year preceding the suicide attempt or the year preceding the interview. Suicide attempters experienced more changes in living situation and caretaker and more repetitions of a class than both other groups. Thirteen (27%) of the suicide attempters reported changes in living situation during the last year, compared with four (6%) of the depressed adolescents and none of the normal adolescents. Six (13%) suicide attempters, compared with one (2%) depressed adolescent and none of the normal adolescents, reported changes in caretaker. Five (10%) suicide attempters, compared with one (2%) depressed adolescent and none of the normal adolescents, reported repeating a class. Five (10%) suicide attempters, compared with two (3%) depressed adolescents and none of the normal adolescents, reported separation of parents. Six (13%) suicide attempters, compared with four (6%) depressed adolescents and none of the normal adolescents, reported changes of residence. Nine (19%) suicide attempters, compared with nine (14%) depressed adolescents and one (2%) normal adolescent, reported mental health events involving family members. Five (10%) suicide attempters, compared with two (3%) depressed adolescents and none of the normal adolescents, reported sexual abuse. The suicide attempters reported a higher mean number of total events than the depressed and normal adolescents (table 3).

Depressed adolescents differed from both other groups in that they reported more physical health events of family members during the preceding year.

**TABLE 3. Mean Number of Major Life Events Experienced During Preceding Year by Adolescents Who Attempted Suicide, Depressed Adolescents, and Normal Adolescents**

| | Suicide Attempters (N=48) | | Depressed Adolescents (N=66) | | Normal Adolescents (N=43) | | Kruskal-Wallis |
|---|---|---|---|---|---|---|---|
| Event | Mean | SD | Mean | SD | Mean | SD | H |
| Serious illness | 0.08 | 0.28 | 0.05 | 0.21 | 0.05 | 0.21 | 0.86 |
| Accident | 0.04 | 0.20 | 0.11 | 0.43 | 0.05 | 0.21 | 0.75 |
| Change in living situation | 0.33 | 0.60 | 0.08 | 0.32 | 0.00 | — | 19.71[a] |
| Change in caretaker | 0.13 | 0.33 | 0.02 | 0.12 | 0.00 | — | 10.57[b] |
| Separation of parents | 0.10 | 0.31 | 0.03 | 0.17 | 0.00 | — | 6.28[c] |
| Reunion of parents | 0.08 | 0.35 | 0.05 | 0.21 | 0.09 | 0.29 | 0.97 |
| Change of residence | 0.17 | 0.48 | 0.06 | 0.24 | 0.00 | — | 6.03[c] |
| Death of family member | 0.00 | — | 0.03 | 0.17 | 0.00 | — | 2.78 |
| Physical health event of family member | 0.04 | 0.20 | 0.36 | 0.72 | 0.07 | 0.34 | 13.71[d] |
| Mental health event of family member | 0.46 | 1.25 | 0.18 | 0.52 | 0.07 | 0.46 | 5.97[c] |
| Unemployment of family member | 0.08 | 0.28 | 0.05 | 0.37 | 0.05 | 0.21 | 2.92 |
| Imprisonment of family member | 0.00 | — | 0.00 | — | 0.00 | — | 0.00 |
| Sibling leaving home | 0.10 | 0.37 | 0.14 | 0.43 | 0.19 | 0.39 | 2.23 |
| Change of school or type of school | 0.17 | 0.43 | 0.12 | 0.37 | 0.07 | 0.26 | 1.40 |
| Repeating a class | 0.10 | 0.31 | 0.02 | 0.12 | 0.00 | — | 8.29[e] |
| Ending a relationship | 0.33 | 0.52 | 0.23 | 0.42 | 0.16 | 0.43 | 3.70 |
| Physical abuse | 0.13 | 0.33 | 0.09 | 0.29 | 0.00 | — | 5.32 |
| Sexual abuse | 0.10 | 0.31 | 0.05 | 0.27 | 0.00 | — | 6.17[c] |
| Criminal events | 0.17 | 0.56 | 0.03 | 0.17 | 0.00 | — | 4.60 |
| Total number of events | 2.63 | 2.88 | 1.67 | 1.29 | 0.79 | 1.01 | 12.01[a] |

[a] $p<0.001$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

[b] $p<0.01$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

[c] $p<0.05$; significant difference between suicide attempters and normal adolescents (Tukey honestly significant difference procedure).

[d] $p<01$; significant difference between depressed adolescents and both suicide attempters and normal adolescents (Tukey honestly significant difference procedure).

[e] $p<0.05$; significant difference between suicide attempters and both depressed and normal adolescents (Tukey honestly significant difference procedure).

Sixteen (24%) of the depressed adolescents reported such an event, compared with two (4%) of the suicide attempters and two (5%) of the normal adolescents.

## DISCUSSION

This study compared adolescent suicide attempters with both depressed and nondepressed adolescents who never made a suicide attempt with respect to the occurrence of life events during childhood, during adolescence, and during the year before the attempt or the year before the date of the interview. In all three time periods, suicide attempters reported more negative life events than did "normal" adolescents. Suicide attempters also reported more negative life events, especially in childhood and during the preceding year, than did depressed adolescents. The overall differences among groups in life events during childhood became larger during adolescence and still larger during the year before the attempt or interview.

In this respect our study seems to confirm the two cited hypotheses of Jacobs (12), who compared adolescent suicide attempters with normal matched control subjects. Our study seems to confirm Jacobs' hypothesis that suicide attempters have a longstanding history of problems during childhood and adds the evidence that this is true not only when suicide attempters are compared with normal subjects but also when they are compared with depressed adolescents. This suggests that the risk of suicide during adolescence might be detected during childhood.

In our comparison of suicide attempters with normal adolescents during adolescence and during the preceding year, our study confirms Jacobs' suggestion that suicidal adolescents experience a period of escalation of problems starting at the onset of puberty. With respect to life events in adolescence, however, our group of depressed adolescents were "in the middle" of the other two groups. During the preceding year, our suicide attempters experienced considerably more problematic life events than did both depressed and normal adolescents.

These results stand for the person-rate frequencies as well as the event-rate frequencies, excluding the possibility that certain statistics may be blurred by the fact that a few individuals in one group experienced an excessive amount of life events. Looking at the type of events, one can observe that suicide attempters suffered from more turmoil in family life during all three time periods. In childhood this was characterized by separation or divorce of parents and unemployment of family members. Under these unstable familial circumstances, characterized by immoderate changes in living situation and caretaker during adolescence, the suicide attempter was characterized by more periods of sexual abuse.

During the last year before the attempt, further social instability—changes in residence and repetition of a class—occurred.

Regarding the finding that adolescent suicide attempters experienced more sexual abuse during adolescence, an extra remark may be appropriate. Our findings, plus those of Deykin et al. (8), suggest that sexual abuse is an important field of attention when dealing with adolescent suicide attempters.

To make a correct estimation of the value of our findings, methodological remarks should be kept in mind. For pragmatic reasons, studying a reasonably large group of adolescent suicide attempters almost requires the use of a retrospective method to investigate changes during childhood. Comments suggest that making use of semistructured interviews may be better than using self-report questionnaires (23) and that predefined events may be more reliable than open-ended questions requiring spontaneous recall. In the present study, both preferable choices were made. In addition, each reported event was discussed in reasonable detail: the interviewer asked when exactly did the event happen, how long did it last, who was involved, etc. This procedure, too, may very well increase reliability. However, adolescents who recently attempted suicide may have a different recollection of various life events, influenced by their mood, for example (24). Apart from the fact that this may apply to depressed adolescents as well, we think it unlikely that children easily forget events such as parental separation or divorce or repetition of a class.

Another possible critique was formulated by Brown (25), who described "retrospective contamination," which for this study suggests that the suicide attempters reported more problematic life events to account for their attempt. In the present study, this might have been the case for the suicide attempters as well as the depressed adolescents, who might have reported more events to account for their depressed mood.

The life events considered here were not studied as causes for suicidal behavior. They are possibly interrelated: one event may lead to another, and they may cluster and have additive effects. For example, the divorce of parents may be related to changes in living situation and caretaker and may precede the reunion of parents. Moreover, this study focused on the importance of life events alone regarding suicidal behavior. Of course, this implies a considerable simplification of processes that adolescents in general and suicidal adolescents particularly go through during childhood and adolescence. For instance, the present study did not investigate any constitutional or neurobiological factors. In addition, psychological variables, which probably have great importance in suicidal behavior (1, 15, 26), were not investigated here. This should be kept in mind when assessing the importance of life events in suicidal behavior.

In spite of these methodological questions, we conclude from these results that adolescent suicide attempters are different from both normal and depressed adolescents with regard to life events. The suicide attempt seems embedded in a situation of not just the problems every adolescent has to deal with but turmoil in family life, already rooted in childhood and not stabilizing during adolescence, in combination with traumatic events during the period of adolescence and social instability in the year preceding the attempt.

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# Psychiatric Correlates of Incest in Childhood

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*Objective: The purpose of the study was to describe more precisely the type of psychiatric illness associated with incest during childhood. Method: The Diagnostic Interview Schedule was administered to 52 adult women who had been victims of incest during childhood and to 23 age- and race-matched comparison subjects from local self-help agencies. Results: The prevalence of 19 psychiatric disorders was higher in the incest group than base population rates. Rates of anxiety disorders (panic disorder, agoraphobia, social and simple phobia), major depression, and alcohol abuse and dependence were significantly higher in the incest group than in the comparison group. More severe types of incestuous abuse were associated with a higher risk for the development of psychiatric disorders. Conclusions: There was an association between incest and psychiatric disorders in this community-based treatment population. All patients, especially those who present with these specific psychiatric disorders, should be queried about childhood sexual abuse during the history.*

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In recent years, literature about child sexual abuse has proliferated. Despite its growing recognition, however, many aspects of child sexual abuse remain poorly understood. Specifically, very little is known about the long-term psychiatric outcome of victims of child sexual abuse in general, and incest in particular.

While the definition of incest is not consistent, for our purposes the medical definition "sexual intercourse or other sexual activity between persons so closely related that marriage between them is legally or culturally prohibited" (1) is most accurate. This includes sexual contact such as fondling of the breasts, buttocks, or vagina, cunnilingus, fellatio, and vaginal or anal intercourse.

Because of its social stigma, the incidence and prevalence of incest have been difficult to measure, in part because of different definitions of abuse and variable makeup of the samples studied. Finkelhor (2), in his survey of 796 college students, found a 28% prevalence of incest (defined as "a sexual experience with a family member") in college women. Half of that was incestuous contact between siblings; of that number, 30% of the sibling incest involved force and was considered exploitative. Twenty-three percent of the sibling incest was perpetrated by siblings 5 or more years older and was also considered exploitative. Thus, approximately 18%–19% of these college women reported exploitative incestuous contact before age 18.

In what is probably the best designed study of the prevalence of incest, Russell (3) interviewed 930 women from a random sample of San Francisco households, finding that 38% had been sexually abused by an adult before the age of 18. Of those, 16% of the total sample (N=152) had been victims of exploitative incest.

Specific information about the psychiatric sequelae of incest is sparse. Finkelhor (4) noted significantly lower levels of sexual self-esteem in both men and women who had been victims of sexual abuse as children, although the nature of the problems these individuals had was not described. Similarly, Herman et al. (5), studying 205 adult women with histories of incest, found that 50.4% believed that the abuse had had significant, long-lasting, negative effects in their lives, while 77.6% noted some long-lasting negative effects. Of the 152 women who had been victims of incest in Russell's survey (3), 53% described the incestuous experience as extremely or very upsetting, and an additional 27% found it somewhat upsetting. Russell concluded that 34% of the victims had experienced extreme trauma, 23% considerable trauma, and 25% some trauma.

Gelinas (6) found three major areas of difficulty among incest victims: "chronic traumatic neuroses, continuing relational imbalances and increased intergenerational risk of incest." Browne and Finkelhor's literature review (7) summarized the long-term effects of childhood sexual abuse including symptoms of depression, anxiety, and substance abuse; self-destructive behavior including suicide attempts; and sexual maladjustment.

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Stein et al. (8), using data from the Los Angeles site of the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study, reported a 6.8% prevalence of childhood sexual abuse in women, well below other estimates. Among the 51 women in the sample who had been victims of child sexual abuse, Stein et al. found a higher prevalence of alcohol abuse and dependence, drug abuse and dependence, major depressive disorder, and phobias. Nearly 60% of the women had at least one diagnosis.

Some authors have reported a correlation between childhood sexual abuse and the development of dissociative disorders. Putnam et al. (9) found that 97% of patients with multiple personality disorder had histories of abuse during childhood. Ross et al. (10) reported that 74.4% of 207 female patients with multiple personality disorder had histories of childhood sexual abuse.

There is also evidence that long-term effects may be influenced by the type of abuse sustained by the victim. Russell (3) demonstrated that more severe forms of sexual abuse produced higher levels of trauma than did fondling or kissing, and both Finkelhor (4) and Russell (3) reported a worse outcome when physical force had been involved. However, the relationship between more traumatic forms of sexual abuse and later development of specific psychiatric syndromes is unknown.

## METHOD

One of us (E.F.P.) contacted all centers in the St. Louis area with specialized programs for sexually abused women, including family service agencies and self-help groups. A psychologist and two social workers known locally to work with sexually abused women were contacted as well. Therapists who agreed to participate in the study agreed that all individuals in therapy would be informed of this study and given the opportunity to participate. In one community-based self-help group run entirely by the participants, one of us (E.F.P.) met with the group, presented information about incest, and offered all group members the opportunity to participate.

All potential subjects were mailed information about the structure and purpose of the research project and were asked to participate. Those who replied were contacted by phone, and interviews were scheduled. Informed consent was obtained before the interview, for which there was no financial remuneration.

Overall, 64% of the subjects who were asked agreed to participate. This rate varied among the individual referral sources, ranging from 43% to 100%. Ninety-three percent of the individuals who agreed to participate were ultimately interviewed. Comparison subjects were age- and race-matched women with no history of physical or sexual abuse and were drawn from the same sources. The consent rate for the comparison subjects was 48%; 89% of those who responded were interviewed. The consent rates did not differ significantly between comparison subjects and incest victims ($\chi^2$=2.88, df=1, n.s.).

**TABLE 1. Abuse Reported by Incest Victims (N=52)**

| Abuse | N[a] | % |
|---|---|---|
| Fondling | 50 | 96.2 |
| Cunnilingus | 18 | 34.6 |
| Fellatio | 19 | 36.5 |
| Sexual intercourse | 19 | 36.5 |
| Unsuccessful attempt at sexual intercourse | 3 | 5.8 |
| Anal intercourse | 6 | 11.5 |
| Pictures[b] | 3 | 5.8 |
| Group sex | 7 | 13.5 |
| Other sexual activity | 4 | 7.7 |

[a] Total is greater than 100% since many subjects reported more than one form of abuse.

[b] Taking sexual pictures or movies of the girl or forcing her to watch pornography.

The final study population included 52 women who had been victims of incest and 23 comparison subjects. Of the incest subjects, 44 (84.6%) were Caucasian, seven (13.5%) were black, and one (1.9%) was Hispanic. The mean±SD age was 36.9±7.0 years. Of the comparison subjects, 21 (91.3%) were Caucasian and two (8.7%) were black. The mean age was 35.9±9.2 years.

For the purpose of this study, incest was defined as unwanted sexual contact between the interviewee and a relative too close to marry, thus excluding so-called mutual exploration between siblings or other peers and inappropriate sexual activity that did not include sexual contact, such as exposure and sexually explicit comments, suggestions, or proposals. This definition did not specify a necessary age difference between the victim and the perpetrator.

All subjects were given a computerized version of the NIMH Diagnostic Interview Schedule (DIS) (11, 12), a structured interview based on *DSM-III* that has been proven to be at least as reliable as individual examinations by psychiatrists in clinical samples (13). Subjects were also asked a set of questions about the incestuous event or events, other sexual abuse, and past use of mental health services.

## RESULTS

The types of abuse reported are listed in table 1. The average number of offenders per victim was 1.8±1.5 (range=1–7, mode=1). The average age at the onset of incest was 6.5±3.3 years. The perpetrator was reported to an authority in seven instances (13.5%); physical force was involved with some of the abuse in 16 cases (30.8%). A history of physical abuse unrelated to the incest, not necessarily by the incestuous abuser, was reported by 31 women (59.6%). Finally, nonincestuous sexual abuse during either adulthood or childhood was reported by 24 of the women (46.2%).

Of 26 possible diagnoses listed in table 2 (with alcohol abuse, alcohol dependence, substance abuse, and

**TABLE 2. Lifetime Prevalence of Psychiatric Illness in Incest Victims and Comparison Subjects**

| | Prevalence in Incest Victims (N=52) | | General Population[a] | | Psychiatric Comparison Subjects (N=23) | | |
|---|---|---|---|---|---|---|---|
| | | | Prevalence | $\chi^2$ | Prevalence | | $\chi^2$ |
| *DSM-III* Diagnosis | N | % | % | (df=1)[b] | N | % | (df=1)[c] |
| Agoraphobia | 23 | 44.2 | 6.83 | 102.26[d] | 4 | 17.4 | 3.889[e] |
| Alcohol abuse or dependence | 15 | 28.8 | 4.99 | 57.39[d] | 1 | 4.3 | 4.337[e] |
| Anorexia nervosa | 1 | 2.0 | 0.11 | 3.40 | 1 | 4.3 | 0.031 |
| Antisocial personality disorder | 8 | 15.4 | 2.04 | 39.75[d] | 0 | 0.0 | 2.511 |
| Atypical bipolar disorder | 7 | 13.5 | 0.61 | 119.79[d] | 0 | 0.0 | 2.009 |
| Bulimia | 12 | 23.1 | — | — | 1 | 4.3 | 2.706 |
| Depression, single episode or recurrent | 46 | 88.5 | 9.50 | 382.40[d] | 23 | 56.5 | 7.884[f] |
| Substance abuse or dependence | 17 | 32.7 | 5.31 | 71.59[d] | 5 | 21.7 | 0.470 |
| Dysthymic disorder | 11 | 21.2 | 5.63 | 20.75[d] | 4 | 17.4 | 0.039 |
| Egodystonic homosexuality | 6 | 11.5 | 0.33 | 163.58[d] | 1 | 4.3 | 0.310 |
| Generalized anxiety disorder | 36 | 69.2 | 12.27 | 151.10[d] | 10 | 43.5 | 3.440 |
| Mania | 1 | 2.0 | 0.90 | 0.003 | 0 | 0.0 | 0.178 |
| Obsessive-compulsive disorder | 9 | 17.3 | 2.62 | 37.79[d] | 1 | 4.3 | 1.332 |
| Panic disorder | 19 | 36.5 | 2.80 | 203.87[d] | 2 | 8.7 | 4.829[e] |
| Pathological gambling | 0 | 0.0 | 0.38 | 0.46 | 0 | 0.0 | 0 |
| Posttraumatic stress disorder | 26 | 50.0 | 1.69 | 689.60[d] | 2 | 8.7 | 9.930[f] |
| Psychosexual dysfunction | 36 | 69.2 | 30.25 | 35.59[d] | 10 | 43.5 | 3.440 |
| Schizophrenia | 2 | 3.8 | 0.58 | 4.75 | 0 | 0.0 | 0.003 |
| Schizophreniform disorder | 0 | 0.0 | 0.03 | 15.37 | 0 | 0.0 | 0 |
| Simple phobia | 26 | 50.0 | 10.63 | 80.54[d] | 3 | 13.0 | 7.692[f] |
| Social phobia | 24 | 46.2 | 2.8 | 340.86[d] | 2 | 8.7 | 8.294[f] |
| Somatization disorder | 7 | 13.5 | 0.29 | 264.34[d] | 0 | 0.0 | 2.009 |
| Tobacco dependence | 22 | 42.3 | 38.97 | 0.12 | 8 | 34.8 | 0.128 |
| Transsexualism | 2 | 3.8 | 0.03 | 12.53[d] | 0 | 0.0 | 0.178 |

[a] Based on St. Louis ECA data for women aged 18–55.
[b] Comparisons between incest victims and expected population prevalence based on St. Louis ECA data.
[c] Comparisons between incest victims and psychiatric comparison subjects.
[d] $p<0.001$.
[e] $p<0.05$.
[f] $p<0.01$.

substance dependence representing four separate diagnoses), the average number of lifetime diagnoses was 7.1±2.3 (range=1–16, mode=5) for the incest victims versus 3.2±3.4 (range=0–9, modes=2, 3, 7) for the comparison subjects. Excluding tobacco dependence, the average number of diagnoses were 6.7±3.4 (range=1–15, mode=5) and 2.8±2.7 (range=0–8, modes=3, 6) for the victims and comparison subjects, respectively (Wilcoxin rank sum, Z=–2.23, p=0.03).

Compared with the lifetime prevalence rates for a comparable group of women aged 18–55 in the St. Louis ECA study, the incest victims had markedly higher lifetime prevalence of most major psychiatric disorders (table 2). In order to allow comparison to the ECA data, alcohol and substance abuse and dependence were combined to make a total of 24 tested diagnoses. The prevalence of bulimia (not tested in the St. Louis ECA study) was also higher than expected rates (14, 15).

The differences in the prevalence of psychiatric disorders were less pronounced when incest victims were compared with other study subjects derived from treatment samples. Nonetheless, incest victims demonstrated a substantially higher lifetime prevalence of agoraphobia, alcohol abuse or dependence, depression, panic disorder, posttraumatic stress disorder (PTSD), simple phobia, and social phobia (table 2). The likelihood of having any psychiatric diagnosis was significantly higher for incest victims than for comparison subjects ($\chi^2$=4.08, df=1, p=0.04).

Among incest victims, those subjected to vaginal intercourse had higher rates of agoraphobia ($\chi^2$=8.73, df=1, p<0.01), simple phobia ($\chi^2$=11.94, df=1, p<0.001), panic disorder ($\chi^2$=11.05, df=1, p<0.001), PTSD ($\chi^2$=8.94, df=1, p<0.005), and somatization disorder ($\chi^2$=6.16, df=1, p<0.05). In cases in which physical force had been used, the victims had a higher prevalence of obsessive-compulsive disorder ($\chi^2$=4.70, df=1, p<0.05), simple phobia ($\chi^2$=7.31, df=1, p<0.01), somatization disorder ($\chi^2$=4.27, df=1, p<0.05), and PTSD ($\chi^2$=7.31, df=1, p<0.01).

Of the 52 incest victims interviewed, 41 (78.8%) had seen at least one mental health professional before their present therapist or group. Of these, 34 (82.9%) felt that their prior therapist had not been helpful. Twenty-eight (53.8%) had never seen a psychiatrist, while 21 (40.4%) stated that they had seen a psychiatrist but did not find him or her to be helpful with their psychiatric problems. Only three (5.8%) stated that they had been treated by a psychiatrist who they felt had been helpful.

## DISCUSSION

As expected, compared to general population rates, women in treatment who had a history of incestuous abuse in childhood reported higher prevalence of virtually every psychiatric disorder investigated other than anorexia nervosa, mania, pathological gambling, and schizophrenia. Much of the higher rate could be attributed to sampling from a treatment population; however, even when compared to age- and race-matched treated comparison subjects, incest victims still demonstrated higher rates of anxiety disorders (agoraphobia, panic disorder, PTSD, and phobias), depression, and alcohol abuse and dependence.

Incest victims also had a significantly higher *number* of diagnoses than did comparison subjects, demonstrating a pattern of greater liability to illness. Since multiple comparisons were made on the same population, it is likely that some of these findings are due to chance. However, the validity of these findings is supported by the results of Stein et al. (8), who found a similar pattern of diagnoses in their sample drawn from a community survey. Our results diverged from those of Stein and co-workers only in that a higher rate of panic disorder was found in the present study, and in the prior study the prevalences of agoraphobia and PTSD were not reported. Absolute rates for the remaining disorders were higher in the St. Louis sample, probably because of differences in recruitment of subjects.

Other studies have indicated that dissociative disorders also may be associated with sexual abuse in childhood. Using the Dissociative Emotive Scale, Bernstein and Putnam (16) reported a correlation between elevated scores and presence of severe dissociative disorders, including multiple personality disorder; this finding was replicated by Ross et al. (17). Similarly, Chu and Dill (18) found that in female psychiatric inpatients, a history of sexual abuse by family members was associated with elevated scores on the Dissociative Emotive Scale, although much of this finding appeared to be accounted for by concomitant physical abuse. Interestingly, in that study, elevated scores on the Dissociative Emotive Scale did not correlate with the clinical diagnosis of a dissociative disorder or PTSD. Because the DIS does not diagnose dissociative disorders, the question of their prevalence in our population must be left unanswered. Future studies of outpatient samples should consider the use of the Dissociative Emotive Scale or similar instrument in order to test the association between childhood sexual abuse and prevalence of dissociative disorders in adulthood. In our population, certain psychiatric disorders were strongly associated with more severe forms of sexual abuse such as intercourse or use of physical force. This finding is consistent with the reports of Russell (3) and Finkelhor (2, 4), who reported greater measures of distress in women who reported more severe forms of abuse.

The incest victims in our group were unlikely to perceive benefit from mental health services in general. Half reported that they had never seen a psychiatrist; of those who had, almost none indicated that they found the experience beneficial. Many of the women volunteered that they had never told their psychiatrists about the abuse, nor were they ever asked. This outcome is made more disturbing by the fact that, excluding tobacco dependence, all subjects had at least one psychiatric disorder and on average met criteria for seven on a lifetime basis. Given the high rates of anxiety disorders and depression, potentially treatable by pharmacotherapy or a combination of psychotherapy and pharmacotherapy, psychiatric intervention might be of unique benefit in this population.

Certain limitations of this study must be kept in mind. First, this was a treatment population, not a random sample of incest victims. However, most of the subjects did not initially approach the agencies from which they were referred with a complaint of having been abused. Instead, the vast majority sought help for psychiatric symptoms or interpersonal problems. Although prior community survey literature does not indicate the percentage of incestuously abused women who have sought help from mental health professionals, this population may overlap with the 57% to 82% who experienced significant trauma as determined in Russell's work (3) or the 50% to 78% of Herman and associates' sample (5) who complained of long-lasting negative effects.

While this study shows an association between incest and psychiatric disorders, it does not explain it. One possibility is that there is a direct causal relationship with incest resulting in trauma which leads to psychiatric problems (including symptoms of depression, anxiety, and poor interpersonal relationships), which in turn bring the individual to treatment. Alternatively, incest could be viewed as a marker for a severely dysfunctional family. It may be that the dysfunctional family environment rather than the incestuous act per se plays a major role in the genesis of interpersonal problems leading to the development of psychiatric symptoms and disorders. In addition, some psychiatric disorders are familial, and the degree of psychiatric illness in the victims' families is unknown.

It could be argued that our study either overestimates or underestimates the true prevalence of psychiatric disorders among incest victims. Because this was a treatment population, victims without any psychiatric distress would have been missed. On the other hand, because we did not include hospitalized inpatients and patients of psychiatrists, the more disordered victims might have been underrepresented. On balance, our population represents women who are troubled and have brought themselves to treatment. Thus, this population focuses on those women who are most likely to both need and seek help.

This study demonstrates a higher prevalence of psychiatric problems in women with more severe types of abuse. It also shows that many victims feel they had not been helped by their psychiatrists or other therapists, perhaps because incest was rarely asked about. Nonetheless, the victims have many potentially treatable psychiatric illnesses. We recommend that childhood sexual abuse be asked about in the initial history, and clinicians should consider repeating this inquiry later, after a therapeutic alliance has been firmly established. To best explicate causal factors of psychiatric illness in incest victims, future research should include large patient samples, be community based, and attempt to ascertain the proportion of women who ever seek help from professionals.

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# Congenital Malformations and Structural Developmental Anomalies in Groups at High Risk for Psychosis

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*Objective: Early somatic developmental anomalies may be one expression of a genetic influence toward psychosis. The purpose of this study was to investigate whether higher rates of early developmental anomalies are associated with heightened genetic risk for psychosis. Method: Rates of congenital malformations and minor structural developmental anomalies were prospectively investigated in 84 high-risk offspring of women with histories of psychosis of nonorganic origin (schizophrenic, schizoaffective, affective, and other psychoses) and in 100 offspring of demographically similar control women with no history of psychosis. Data were collected by means of multiple physical examinations through the first 3–4 years of the offspring's lives. Results: The rates of total congenital malformations were high, but the great majority of these malformations in both the index group and the control group represented minor physical aberrations. Rates of congenital malformations in the offspring of the index women (or any specific diagnostic subgroup of these women) were not different from those in the offspring of the control women. Conclusions: The inferred genetic risk for psychosis does not appear to be associated with greater rates of early somatic developmental anomalies, suggesting that early developmental anomalies do not represent an expression of genetic influence toward psychosis.*

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Evidence suggests increasingly that somatic trauma to the fetus and/or maldevelopment of the offspring during pregnancy or the perinatal period are in some manner associated with the development of psychosis in the same offspring in adulthood (1–6). The relation between early trauma/maldevelopment and later psychosis appears to involve primarily schizophrenia, but some data also suggest an association with schizoaffective (6) and bipolar affective (2) disorders. The specific role of maternal obstetric complications in the development of schizophrenia and other psychoses in the offspring, as well as the relation between obstetric complications and genetic factors, remains to be determined. Perhaps the most likely interpretation of the greater rates of maternal obstetric complications or early developmental anomalies among prepsychotic offspring is that these phenomena represent early fetal trauma, with neurobiological consequences which contribute to the later development of psychosis. An alternative interpretation is that the obstetric complications or developmental anomalies are merely an expression of genetic influence (7–10) or a secondary correlate of other parental environmental influences (4). If the latter were true, obstetric complications would be an epiphenomenon (i.e., a consequence or correlate of psychosis) rather than a primary "somatic trauma" factor contributing to the development of psychosis.

One strategy available at present for investigating the hypothesis that early trauma/developmental anomalies are a direct or indirect expression of genetic influence toward psychosis is to study the rate of early trauma and developmental anomalies in groups of individuals at greater genetic (and perhaps environmental) risk for the psychiatric disorders of interest (11). Numerous such studies have been done regarding maternal obstetric complications, and the extensive evidence obtained to date indicates clearly that pregnancy and birth complications of the type typically registered by prenatal and obstetric services do *not* occur unusually frequently among offspring who are at greater genetic risk for psychoses (4–6, 12). This suggests that neither genetic factors nor the many other possible environmental factors directly associated with parental psychosis influence the occurrence of obstetric complications of the type related to risk for schizophrenia in offspring. Thus, obstetric complications do not appear to represent an epiphenomenon.

In contrast, there appears to be little empirical evi-

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dence concerning whether congenital malformations, including minor structural developmental anomalies, occur unusually frequently among individuals at heightened genetic (and environmental) risk for psychosis. To our knowledge, only three studies have systematically investigated the rates of congenital malformations in the offspring of parents with psychosis. Sobel (13) used psychiatric records to investigate rates of malformations occurring in 222 offspring of schizophrenic women who were in New York state mental hospitals at the time of delivery in 1950–1958. He reported a higher rate of malformations in these offspring (3.2%) than in two separate samples from the general population (about 1%). Similarly, Rieder et al. (14) found that there were significantly more deaths associated with neurological malformations among offspring of parents with various psychiatric illnesses (1.9%) than among offspring of control parents (0%). In contrast, Paffenbarger (15) found no difference in rates of congenital defects between the offspring of 126 women with postpartum psychosis and the offspring of control women (no specific rates of congenital malformations were given for either group). Reports from two other studies (16, 17) included mention of several specific congenital malformations found among the offspring of schizophrenic parents, but no group rates of congenital malformation per se were cited for the samples. The greater frequencies of congenital malformations in high-risk offspring reported in the studies by Sobel and Rieder et al. were thus associated with rather severe conditions (childbirth in mental hospitals, congenital malformations associated with death of the offspring) and represented rather minimal increases in the rates of these malformations (2%–3%) as compared with low control group rates (0%–1%).

Furthermore, the studies to date appear to have included only major congenital malformations. Considerable scientific interest has more recently been directed toward congenital aberrations termed "minor physical anomalies." Minor physical anomalies are minor congenital malformations found primarily in the ectoderm (18, 19); they develop during the first trimester of pregnancy as a result of genetic or other teratogenic factors. Minor physical anomalies may represent signs of early developmental anomaly occurring at approximately the same gestational time as major CNS development. Furthermore, since many minor physical anomalies develop in the same embryonic layer as does the CNS, minor physical anomalies might represent an externally visible sign of parallel developmental deviation in the CNS itself (18, 19). Evidence suggests that minor physical anomalies occur with greater frequency among persons with schizophrenia, autism, mental retardation, hyperactive or inhibited behavior, learning difficulties, and speech and hearing difficulties (3, 18–23), thus supporting a coupling of early developmental anomaly and the subsequent development of a range of different mental disorders.

Further study of the rate of both major congenital malformations and minor developmental anomalies among offspring at high risk for psychosis is therefore indicated. Data collected in our prospective study of the offspring of pregnant women with histories of psychosis and the offspring of pregnant control women with no history of psychosis (24) provided the opportunity to investigate this topic in several maternal psychosis groups and demographically similar control groups. The data on congenital malformations were obtained from examinations conducted on numerous occasions during the offspring's first several years of life, thus providing a long-term assessment of somatic developmental anomalies that reflect pre- or perinatal maldevelopment. The hypothesis tested was that the offspring of women with psychosis more frequently have congenital malformations than do the offspring of normal control women.

## METHOD

The index sample consisted of 84 offspring of pregnant women who registered at the comprehensive prenatal clinics in southern Sweden during a 4.5-year sampling period (1973–1977), who had histories of hospitalization for nonorganic psychosis before the current pregnancy, who participated in the longitudinal study (24), and for whose offspring information was available concerning the presence of congenital malformations. Table 1 shows the distribution of the maternal psychiatric diagnoses in the 84 cases according to the Research Diagnostic Criteria (RDC) (25) and the project's own diagnostic criteria (24). Project criteria include schizophrenic, cycloid, affective, and other, "nonendogenous" psychoses. The RDC definitions of schizophrenic disorders and affective disorders (manic, bipolar, and major depressive) are broader than the project criteria for these two types of disorders, and the RDC schizophrenic and affective disorder subjects included all project-criteria schizophrenic and affective disorder subjects, respectively, plus a number of subjects from the project-criteria "other psychoses" group. The use of the two diagnostic systems in parallel provides the opportunity to study the effects of breadth of diagnostic definitions on study results (26, 27).

The control sample consisted of 100 offspring of pregnant women with no history of psychosis who were matched with the women in the index sample with respect to the clinic at which they received prenatal care, maternal parity, age, social class, and marital status during pregnancy; who participated in the longitudinal study (24); and for whose offspring there was information regarding congenital malformations. Each diagnostic group had its own matched control group.

Informed consent was obtained after the procedures had been fully explained. Only one perinatal death (of a control subject) and no postnatal deaths occurred in the samples.

Information concerning congenital malformations in the entire group of 184 offspring was obtained from well-baby clinic records covering repeated physical ex-

**TABLE 1. Rates of Congenital Malformations in Offspring of Mothers With Histories of Nonorganic Psychosis and in Matched Control Subjects**

| | | Malformation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | None | | Some | | Variant | | Minor | | Major | |
| Group | N | N | % | N | % | N | % | N | % | N | % |
| Total index | 84 | 54 | 64 | 30 | 36 | 15 | 18 | 9 | 11 | 6 | 7 |
| Total control | 100 | 61 | 61 | 39 | 39 | 23 | 23 | 9 | 9 | 7 | 7 |
| Mother's diagnosis according to RDC | | | | | | | | | | | |
| Schizophrenia | 33 | 23 | 70 | 10 | 30 | 4 | 12 | 2 | 6 | 4 | 12 |
| Matched control | 39 | 19 | 49 | 20 | 51 | 13 | 33 | 3 | 8 | 4 | 10 |
| Schizoaffective disorder | 15 | 10 | 67 | 5 | 33 | 3 | 20 | 2 | 13 | 0 | 0 |
| Matched control | 16 | 11 | 69 | 5 | 31 | 2 | 13 | 2 | 13 | 1 | 6 |
| Affective disorder | 26 | 15 | 58 | 11 | 42 | 6 | 23 | 3 | 12 | 2 | 8 |
| Matched control | 30 | 22 | 73 | 8 | 27 | 5 | 17 | 2 | 7 | 1 | 3 |
| Unspecified functional psychosis | 10 | 6 | 60 | 4 | 40 | 2 | 20 | 2 | 20 | 0 | 0 |
| Matched control | 15 | 9 | 60 | 6 | 40 | 3 | 20 | 2 | 13 | 1 | 7 |
| Mother's diagnosis according to project criteria | | | | | | | | | | | |
| Schizophrenia | 16 | 11 | 69 | 5 | 31 | 3 | 19 | 1 | 6 | 1 | 6 |
| Matched control | 22 | 12 | 55 | 10 | 45 | 5 | 23 | 2 | 9 | 3 | 14 |
| Cycloid psychosis | 15 | 10 | 67 | 5 | 33 | 2 | 13 | 2 | 13 | 1 | 7 |
| Matched control | 18 | 11 | 61 | 7 | 39 | 5 | 28 | 1 | 6 | 1 | 6 |
| Affective illness | 14 | 8 | 57 | 6 | 43 | 3 | 21 | 3 | 21 | 0 | 0 |
| Matched control | 18 | 12 | 67 | 6 | 33 | 3 | 17 | 2 | 11 | 1 | 6 |
| Psychogenic psychosis | 6 | 3 | 50 | 3 | 50 | 1 | 17 | 2 | 33 | 0 | 0 |
| Matched control | 7 | 4 | 57 | 3 | 43 | 2 | 29 | 1 | 14 | 0 | 0 |
| Postpartum psychosis | 16 | 10 | 63 | 6 | 38 | 5 | 31 | 0 | 0 | 1 | 6 |
| Matched control | 18 | 10 | 56 | 8 | 44 | 3 | 17 | 3 | 17 | 2 | 11 |
| Other psychoses | 17 | 12 | 71 | 5 | 29 | 1 | 6 | 1 | 6 | 3 | 18 |
| Matched control | 17 | 12 | 71 | 5 | 29 | 5 | 29 | 0 | 0 | 0 | 0 |

aminations during the first 3–4 years of life (28). In addition to these routine pediatric examinations, all but 13 of the infants were also examined by one or more project researchers; the first author examined 154 infants at delivery, and 127 were examined by the second author on the third or fourth day postpartum. In 11 of the 13 cases in which the infant was not seen by a project researcher, information about the child's condition was obtained from clinic personnel at the time of delivery. The current study included systematic evaluation for not only major congenital malformations but also minor congenital malformations and minor physical anomalies such as birthmarks, simian line, sacrococcygeal pits, etc.

All congenital malformations identified through these three sources were classified (by the third author) according to the system of Ekelund et al. (29) as representing variants, minor structural abnormalities, or major congenital malformations; the last were further subdivided into dubious or insignificant type and gross type. In table 1 and in the statistical analyses, if a child had multiple congenital malformations belonging to more than one of these three categories, classification of the child as having major congenital malformations was given priority over classification as having minor congenital malformations or variants, and minor congenital malformations were given priority over variants.

The frequency of offspring having no congenital malformation versus those having some congenital malformation was analyzed statistically for both the total index sample and each diagnostic group and its matched control subjects with the use of chi-square and Fisher's exact probability tests. The hypothesis indicated one-tailed analyses.

## RESULTS

### *Congenital Malformations in the Total Sample of Index Plus Control Offspring*

The rates of total congenital malformations and the frequencies of subjects categorized as having no congenital malformations, variants, minor congenital malformations, and major congenital malformations are shown in table 1. The nature and frequencies of the specific congenital malformations observed in the index group and the control group are shown in table 2.

Among the total 184 offspring, 69 (38%) had at least one congenital malformation, and eight (4%) had two. More than half (58%, N=45) of the total congenital malformations (N=77) in these 184 offspring belonged to the variant category, while 25% (N=19) represented minor congenital malformations, and 17% (N=13) were major congenital malformations. A number of the major malformations identified (positive Ortolani's sign, cardiac murmur, pyloric stenosis) belonged to the subgroup termed "dubious or insignificant" by Ekelund et al. (29), and only a few subjects (2%, N=4 of 184) had major congenital malformations of the gross type (table 2). Among the 18 subjects with minor congenital malformations, one had two different minor malformations and four others also had malformations classified as variants. Three of the 38 subjects with only

**TABLE 2. Frequencies of Specific Congenital Malformations in Offspring of Mothers With Histories of Nonorganic Psychosis and in Matched Control Subjects**

| Malformation | Index Group (N=84) | Control Group (N=100) |
|---|---|---|
| Variant | | |
| Hemangioma | 5 | 12[a] |
| Nevus | | 2[a] |
| Undescended testes | 1 | 2 |
| Umbilical hernia | 3 | 2 |
| Inguinal hernia | 2 | 1 |
| Hydrocele | 1 | 3 |
| Strabismus | 3 | 3 |
| Simian line | 2 | 2[a] |
| Epicanthus folds | | 1[a] |
| Minor structural abnormality | | |
| Slight ear dysplasia | 2 | 2 |
| Minor malpositions of feet/toes/ fingers; syndactyly | 2 | 5 |
| Sacrococcygeal pits | 3 | 1 |
| Minor genital malformations | 1 | 1 |
| Open fontanel at 2.5 years | 1 | |
| Slight facial dysplasia and suspected ocular albinism | 1 | |
| Major congenital malformations | | |
| Dubious or insignificant type | | |
| Positive Ortolani's sign (treated) | 4 | 2 |
| Cardiac murmur | | 2 |
| Pyloric stenosis | 1 | |
| Gross type | | |
| Pes calcaneovalgus | | 2 |
| Pes equinovarus | 1 | |
| Hypospadias | | 1 |

[a] One subject also had a congenital malformation classified as a minor abnormality and was counted in that group.

variants had two different congenital malformations. All subjects with major congenital malformations had only one malformation each.

### *Congenital Malformations in the Index Versus the Control Offspring*

As shown in table 1, the index and control groups were very similar to each other in rates of total congenital malformations, variants, minor congenital malformations, and major congenital malformations. Division of the sample according to the different maternal psychiatric diagnostic subgroups and their demographically matched control groups yielded quite small subgroups with congenital malformations, but the data suggested that the rates of malformations for the specific diagnostic groups were not notably different from those for their respective control groups. Diagnosis of maternal psychosis according to the RDC versus the project criteria led to no notable differences in rates of congenital malformations among the offspring of mothers with schizophrenic, schizoaffective/cycloid, and affective disorders. Furthermore, the specific types of congenital malformations found in the total index group were well distributed across the different psychiatric diagnostic subgroups. No significant difference was found on any of the statistical comparisons, and the hypothesis of greater rates of congenital malformations in index cases was not supported by the results.

## DISCUSSION

In this prospective study, offspring of women with histories of nonorganic psychosis were found not to differ from offspring of normal control women in rates of congenital malformations classified in several different ways. This absence of index-control differences was not due to an insufficient frequency of congenital malformations in the samples. More than one-third of the offspring in the combined index and control samples had one or more of the broad range of physical deviations classified as congenital malformations, and 7% had major congenital malformations.

The rates of congenital malformations observed in a sample will be influenced by the intensity of scrutiny and examination during a given period, the length of follow-up, and the breadth of physical deviations subsumed within the concept of congenital malformations and developmental anomalies. The very high rate of total congenital malformations observed in both the index and control samples was likely due to all of these factors. 1) A broad range of aberrations was intentionally selected for inclusion among congenital malformations, and indeed a great majority (83%) of the malformations identified were variants or minor structural abnormalities, while only 17% were major classical congenital malformations, and even fewer (5%) were gross major congenital malformations. 2) Congenital malformations were identified through multiple examinations, including extra neonatal physical examinations done for research purposes and with special attention paid to minor deviations. 3) The data reflected a long observation time for the identification of congenital malformations, that is, the first 3–4 years of life; previous studies indicate that the rate of identified malformations doubles if children are followed up through 5 years of age rather than just examined perinatally (30). Furthermore, the possibility that factors which increase the risk of congenital malformations were found in both samples cannot be excluded. For example, both index and control mothers were unusually old at the time of these births (24).

Whatever the reasons for the high total rates of congenital malformations, the identification procedure was applied in a comparable manner to the index and control groups, and the two groups were found not to differ in these rates. Because the rates in the index and control groups did not differ, further possible analyses to determine any relations between these malformations and other factors such as maternal obstetric complications and maternal medication during pregnancy are not indicated, as might have been the case if the index subjects had had higher rates of congenital malformations.

The similar rates of congenital malformations in the index and control groups could be interpreted in several different ways. There could be a relation between greater genetic risk and the occurrence of congenital malformations, but this relationship would not be discernible in the present study because too few of these high-risk offspring would have the gene (or genes) for psychosis. Unfortunately, there is no certain knowledge about the true frequency of psychosis-related genes in the offspring of, for example, one schizophrenic parent (31). Although the true rate of expected gene carriers in our offspring samples cannot be estimated prior to identification of the psychosis-related gene (or genes) or the true genetic mode of inheritance, the frequency of gene carriers could, nevertheless, have well exceeded the rate of expected psychotic cases in these offspring groups (10%–25%) (24). For example, relatively low rates of concordance for schizophrenia have been observed in modern studies of monozygotic twins (32), and these pairs by definition have a genetic makeup that is "sufficient" to permit the development of schizophrenia in at least one of the twins.

Whatever the true rate of gene carriers in the index offspring, an existing relationship between psychosis-related genes and congenital malformations should have led to at least a nominally greater rate of congenital malformations in the index group than in the control group, but this was clearly not the case in the current findings. Moreover, the offspring of the schizophrenic mothers tended to show notably lower rates of congenital malformations than did the offspring of their matched control subjects (table 1), and schizophrenia is the disorder for which the most evidence of early trauma and maldevelopment exists (1–6).

In contrast, the findings appear more to suggest that there is no relation between greater genetic risk and the occurrence of congenital malformations. If this interpretation is true, then the congenital malformations that are observed with greater frequency among persons who become schizophrenic are not the result of genetic influence associated with that disorder but, rather, are the result of other teratogenic influences of possible etiological relevance for psychosis.

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# Wisconsin Card Sorting Test Performance in Schizophrenia: Remediation of a Stubborn Deficit

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*Objective: Schizophrenic patients typically perform poorly on the Wisconsin Card Sorting Test, which is a putative index of prefrontal functioning. The authors attempted to remediate the deficits of schizophrenic patients on this measure by giving detailed instructions and monetary reinforcement. Method: Forty-six inpatients with chronic schizophrenia and 20 control subjects with other psychiatric illnesses were given the Wisconsin Card Sorting Test under four conditions that varied in monetary reinforcement and level of instructions. The schizophrenic patients were given the Brief Psychiatric Rating Scale (BPRS) and three information processing measures (the Continuous Performance Test, Span of Apprehension, and Pin Test). Results: Schizophrenic patients performed worse than psychiatric control subjects across most conditions. Monetary reinforcement had little effect on performance, but detailed instructions significantly improved the scores for both groups. When instructions were withdrawn and monetary reinforcement was maintained, both groups continued to show improved performance over baseline. Symptoms were not significantly associated with Wisconsin Card Sorting Test performance. One measure (the Pin Test) correlated significantly with performance on the Wisconsin Card Sorting Test. Conclusions: The results suggest the importance of combining motivational with instructional factors for training psychiatric patients in problem solving.*
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The Wisconsin Card Sorting Test has attracted considerable attention from schizophrenia researchers recently. The amount of interest directed at this measure is somewhat surprising given that the Wisconsin Card Sorting Test is not new (it was developed in 1948 by Grant and Berg [1] and later modified by Milner [2]) and does not require high technology (simply a set of 128 cards). The Wisconsin Card Sorting Test requires subjects to match cards to one of four target cards on the basis of three rules (color, shape, or number of objects). The subjects are not told how to match the cards; they are simply told whether the match was correct or not. Based on this information, they are to figure out the correct sorting rule. If a subject makes 10 consecutive correct matches, the sorting rule changes without warning, and the subject needs to determine the new principle. To be successful on the Wisconsin Card Sorting Test, subjects need to 1) *attain* a concept (or rule), 2) *maintain* that concept for 10 consecutive trials, and 3) *switch* the concept when the rules for sorting change.

Much of the current interest in the Wisconsin Card Sorting Test rests on the hypothesis that the Wisconsin Card Sorting Test is a selective measure of frontal functioning (specifically, dorsolateral prefrontal functioning). Evidence that the Wisconsin Card Sorting Test assesses prefrontal functioning comes from two types of paradigms: lesion studies and activation studies. Several lesion studies with neurological patients (2, 3) have found that lesions to the prefrontal cortex have an especially adverse effect on test performance. Although this finding is widely reported, some studies have implicated the orbitomedial instead of the dorsolateral regions (4, 5), and other studies (6; unpublished 1990 paper of S.W. Anderson et al.) have failed to find a correspondence between frontal lesions and deficits on the sorting tests.

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In addition to lesion studies, activation studies have examined metabolic changes that accompany Wisconsin Card Sorting Test performance. Two elegant studies of regional cerebral blood flow (7, 8) reported that the metabolic activity in the dorsolateral prefrontal region increased in normal control subjects but not in schizophrenic patients when performing the Wisconsin Card Sorting Test. In addition, better performance for the schizophrenic patients correlated with greater metabolic activation in the dorsolateral prefrontal region. Although dysfunctions in other regions may impair Wisconsin Card Sorting Test performance (7), these findings were consistent with the hypothesis that a prefrontal defect impaired the performance of schizophrenic patients on the Wisconsin Card Sorting Test.

The question remains whether schizophrenic patients can improve their performance, presumably by activating the prefrontal region. In a study of schizophrenic children, Schneider and Asarnow (9) gave the Wisconsin Card Sorting Test without instructions for the first half (64 cards). The three sorting principles were then explained and demonstrated before administering the second half of the test. There was a tendency toward a reduction in the number of perseverative responses on the second half of the test, but the number of nonperseverative errors significantly increased after instruction, suggesting that additional task-relevant information can impair the performance of schizophrenic subjects.

In a study of adults with chronic schizophrenia, Goldberg et al. (10) reported that patients with extreme deficits on the Wisconsin Card Sorting Test improved their performance when they received trial-by-trial instructions. The instructions included information about the different categories and the shifting of the set. The improvement was not surprising because the experimenter essentially served as a surrogate frontal lobe for the subject. Interestingly, once the instructions were withdrawn the patients returned to their baseline deficit level of performance. This pattern suggested that schizophrenic subjects have a deficit on the Wisconsin Card Sorting Test that is not remediable.

These results are somewhat discouraging; they suggest that schizophrenic patients are not able to benefit from training in a problem-solving task. Because many of the current rehabilitation programs require patients to learn problem-solving techniques (11), the conclusions of Goldberg et al. challenge a central premise of psychiatric rehabilitation. However, before final conclusions are drawn, additional behavioral and/or motivational paradigms should be attempted.

Bellack et al. (12) successfully trained a small group of 12 schizophrenic patients on the Wisconsin Card Sorting Test. The subjects of Bellack et al. were less impaired and were given more sophisticated training than the subjects of Goldberg et al. For example, the subjects of Bellack et al. were given a longer training period and a shorter baseline period to minimize failure. Because the two studies (both of which await replication with larger groups of subjects) differed in both the severity of the patients' illness and the training procedure, it is not known which variable accounted for the successful training. In support of the idea that patient characteristics might influence performance, Braff et al. (13) found that outpatients with schizophrenia showed relatively mild deficits on the Wisconsin Card Sorting Test.

Bellack et al. did not find that monetary reinforcement without instructions improved performance on the Wisconsin Card Sorting Test. However, a recent report by Summerfelt et al. (14) found that monetary reinforcement alone was sufficient to improve performance on the Wisconsin Card Sorting Test. Hence, the role of monetary reinforcement remains unclear.

These studies raise several important questions: 1) By modifying the training procedure, can chronic, severely impaired patients be trained on the Wisconsin Card Sorting Test? 2) Do patients with psychiatric disorders other than schizophrenia show a different rate of improvement than patients with schizophrenia? and 3) What are the symptom and information processing correlates of Wisconsin Card Sorting Test performance? The present study describes an attempt to remediate the deficits of inpatients with chronic schizophrenia and psychiatric control subjects on the Wisconsin Card Sorting Test through monetary reinforcement and detailed instructions. In addition, we explored the symptom and information processing correlates of Wisconsin Card Sorting Test performance.

## METHOD

### *Subjects*

Forty-six patients with schizophrenia (33 men and 13 women) and 20 control subjects with other psychiatric illnesses (11 men and nine women) were tested on a computerized version of the Wisconsin Card Sorting Test. Partial Wisconsin Card Sorting Test data were collected from one patient with schizophrenia. All subjects gave informed consent after the procedures were fully explained. All were drawn from inpatient units of a state hospital.

All schizophrenic patients met *DSM-III-R* criteria for schizophrenia based on a version of the Present State Examination (15) supplemented with items from the Schedule for Affective Disorders and Schizophrenia (16). Interviewers were trained to a sensitivity of at least 0.85 and a specificity of at least 0.90 for key psychotic and affective symptoms in a university clinical research center for the study of schizophrenia. Potential subjects were excluded if they had a history of drug or alcohol dependence, an identifiable neurological disorder, or any signs of mental retardation (IQ less than 70) or if they were over 55 years of age. The study group was fairly chronic and received relatively large doses of neuroleptic medication (table 1).

The psychiatric control subjects were drawn from the same units as the schizophrenic patients, but they had chart diagnoses of substance abuse, substance dependence, or affective disorder without psychotic features.

**TABLE 1. Characteristics of Patients With Schizophrenia and Psychiatric Control Subjects Given the Wisconsin Card Sorting Test**

| Characteristic | Schizophrenic Subjects (N=46) | | Psychiatric Control Subjects (N=20) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 33.9 | 7.5 | 20.7 | 7.4 |
| Education (years) | 11.8 | 1.9 | 10.4 | 1.4 |
| Age at first hospitalization (years) | 20.3 | 4.4 | — | — |
| Time since first hospitalization (years) | 13.6 | 5.7 | — | — |
| Neuroleptic medication (mg/day, chlorpromazine equivalents) | 1097 | 815 | — | — |

Table 1 lists the available demographic data for both patient groups.

### *Symptom Ratings*

Symptom ratings for schizophrenic patients were based on an expanded version of the Brief Psychiatric Rating Scale (BPRS) (17). All raters were trained to a reliability of at least 0.80 (according to the median intraclass correlation coefficient) by the diagnostic unit of our clinical research center. Three indexes were derived from items on the expanded BPRS: 1) the psychotic index included unusual thought content, hallucinations, and conceptual disorganization, 2) the withdrawal/retardation index included blunted affect, motor retardation, and emotional withdrawal, and 3) the depression index included depressive mood, guilt, and suicidality.

### *Wisconsin Card Sorting Test*

A computerized Wisconsin Card Sorting Test (developed by Wang Neuropsychological Laboratory) was administered on an IBM PC-XT with a Taxan 720 color monitor. Subjects were shown a card and asked to match it by pointing to one of four target cards displayed on the monitor. An experimenter then pressed the button corresponding to the selected target card. The Wisconsin Card Sorting Test was administered in a single session to all subjects under four conditions (64 trials each) in the following order.

*Condition 1: baseline administration.* As recommended by Heaton (18), no information was provided to the subjects about the matching strategy.

*Condition 2: monetary reinforcement only.* Immediately after every correct response, two pennies were dropped into a bowl located next to the subject.

*Condition 3: monetary reinforcement plus detailed instructions.* Subjects continued to receive two cents for every correct response. In addition they received trial-by-trial instructions that were designed to approximate those used by Goldberg et al. (10). Subjects were told about the sorting principles ("There are three ways to match the cards: you can match the card by color, by the number of objects on the card, or by shape"). If the subject completed one set, he or she received additional instructions about the change of rules ("After you get 10 correct in a row, the rule changes; you are no longer matching to color, you must be matching to the number of objects or the shape"). After each correct answer, the subjects were told why it was right ("That's right, we are matching to color"), and after each wrong answer they were told the alternative sets ("That was wrong so we are not matching to the number of objects, we must be matching to color or shape").

*Condition 4: monetary reinforcement only.* This condition was identical to condition 2; the instructions were withdrawn and subjects continued to receive monetary reinforcement.

Dependent measures for the Wisconsin Card Sorting Test included the total number of correct responses (out of 64), the number of categories (sets) completed, and perseverative errors for each condition. Perseverative errors were scored according to the method of Heaton (18).

### *Information Processing Measures*

A subgroup of 27 of the schizophrenic patients were also included in a separate protocol and received three information processing tests and the BPRS.

*Pin Test.* The Pin Test (19) is a motor sequencing test that measures neuromotor speed and dexterity. Subjects sat in front of a small metal template with a series of holes drilled through it in a sinusoidal pattern. They were instructed to use a straight pin to quickly punch holes through the template into a piece of resistance cardboard and a recording sheet of paper placed between the template and cardboard. Subjects performed this twice with each hand for 30 seconds. The dependent measure was the average number of pin holes for each hand.

The other two information processing measures were presented on an IBM-PC computer with a Taxan 720 color monitor. Viewing distance was 1 m, and subjects responded by pressing a response button.

*Degraded-Stimulus Continuous Performance Test.* The Degraded-Stimulus Continuous Performance Test is a measure of visual vigilance (20). Version 1 of the UCLA Continuous Performance Test computer program was used (unpublished manual and program by K.H. Nuechterlein and R.F. Asarnow). Subjects were instructed to press a response button whenever they saw the target number, zero. The numbers were degraded to a standardized degree by randomized pixel reversal. Subjects were shown a series of 160 practice trials followed by 480 experimental trials. For all trials, the stimuli were presented for 60 msec at 1-sec intervals. The target zero appeared in a quasi-random sequence 20 out of every 80 trials.

The dependent measures for the Degraded-Stimulus Continuous Performance Test included vigilance level (a measure of signal-to-noise discrimination measured by the nonparametric statistic A') and vigilance decrement (the change in vigilance level calculated by subtracting A' of the last third of the test from the first third).

*Span of Apprehension.* The Span of Apprehension is an index of early iconic memory and readout stages of visual processing (21). Version 1 of the UCLA Span of Apprehension computer program was employed (unpublished 1987 manual and program by R.F. Asarnow and K.H. Nuechterlein). Subjects were told that letters would be flashed on the screen and that either the letter T or the letter F would be in each array. Either two or 11 nontarget letters were placed randomly in other positions of the array. Each array size was presented in blocks of 16 trials, and an equal number of Ts and Fs appeared within each block. Four blocks of each size array were administered. Subjects received 20 practice trials to become familiar with the procedure.

Due to a ceiling effect for the smaller array, only the results for the larger array were considered in the current study. The dependent measures were the number of correct responses and the mean reaction time for correct responses.

### Statistical Analyses

To examine the effects of the conditions, two-factor (group by condition) analyses of variance (ANOVAs) were conducted for each of the three measures from the Wisconsin Card Sorting Test (number correct, perseverative errors, and number of categories completed). The Greenhouse Geisser probabilities were used for all within-subjects analyses. Follow-up comparisons were made when appropriate. In the presence of interactions, main effects are cited only if they are ordinal (i.e., consistent across levels of the other factor) (22, p. 204).

For examining the relationships between information processing, symptoms, and measures from the Wisconsin Card Sorting Test, Pearson product-moment correlations were used.

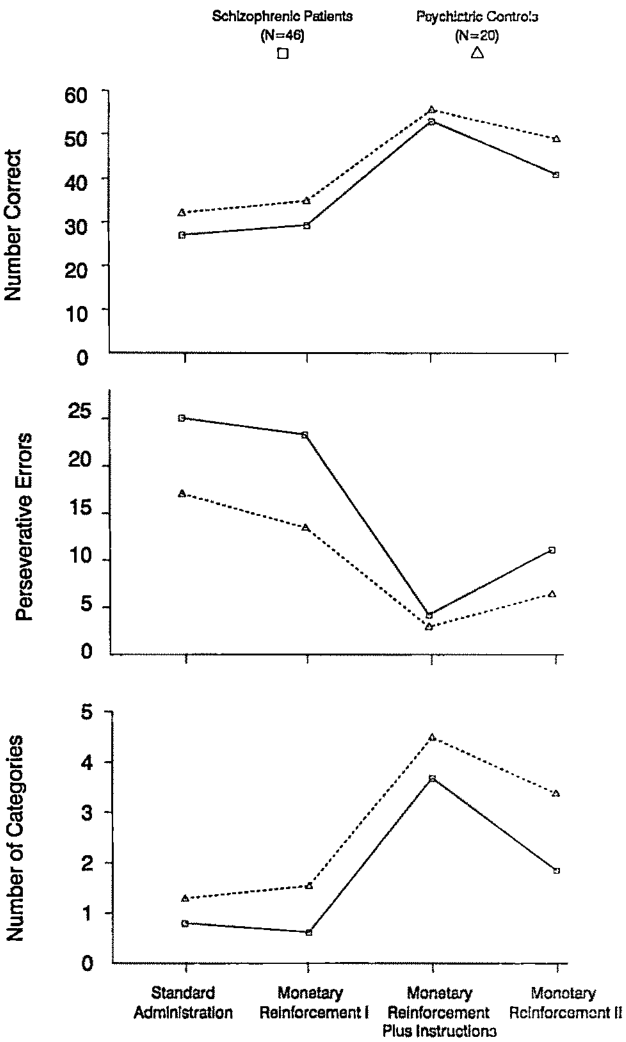
## RESULTS

### Training on the Wisconsin Card Sorting Test

For baseline, condition 1, the mean scores for the schizophrenic patients were $27.2\pm10.7$ for number correct, $25.1\pm13.9$ for perseverative errors, and $0.80\pm1.1$ for categories completed. The psychiatric control subjects showed a trend for better performance than the schizophrenic patients for number correct ($32.1\pm11.4$) ($t=1.70$, df=64, $p=0.09$) and categories completed ($1.3\pm0.9$) ($t=1.73$, df=64, $p=0.09$), and their scores were significantly better for perseverative errors ($17.1\pm12.7$) ($t=2.22$, df=64, $p<0.05$). These data are illustrated in figure 1.

*Number correct.* The effect for condition ($F=123.5$, df=3, 189, $p<0.0001$) and the effect for group ($F=7.51$, df=1, 63, $p<0.01$) were significant for the total number correct. The interaction was not significant ($F=1.20$). In the absence of an interaction, the two groups were combined for comparisons with baseline. The scores from conditions 3 and 4 were significantly higher ($p<0.0003$ after Bonferroni correction) than baseline, but the scores from condition 2 did not differ from baseline.

**FIGURE 1. Performance of Schizophrenic Patients and Psychiatric Control Subjects on the Wisconsin Card Sorting Test Under Four Conditions**



*Perseverative errors.* The effect for condition ($F=57.1$, df=3, 189, $p<0.0001$), the effect for group ($F=8.88$, df=1, 63, $p<0.01$), and the group by condition interaction ($F=3.11$, df=3, 189, $p<0.05$) all reached significance for perseverative errors. Comparisons with baseline were conducted separately for each group. The results followed the same pattern for both groups: scores from conditions 3 and 4 were significantly better than those from baseline ($p<0.006$ with Bonferroni adjustment), but the scores from condition 2 were not significantly different from baseline. The significant interaction can be attributed to a trend ($F=3.53$, df=1, 64, $p=0.065$) for the groups to differ less at condition 3 than at condition 1 (likely due to a floor effect on condition 3).

*Categories.* The ANOVA for the number of completed categories showed significant effects for condition ($F=118.2$, df=3, 189, $p<0.0001$), group ($F=15.67$, df=1, 63, $p<0.0005$), and group by condition interac-

**TABLE 2. Correlations Between Number Correct on the Wisconsin Card Sorting Test and Information Processing Measures for 27 Schizophrenic Patients**

| | Correlation (r)[a] | | |
|---|---|---|---|
| Measure | Standard Administration (Condition 1) | Monetary Reinforcement II (Condition 4) | Partial Correlation[b] |
| Degraded-Stimulus Continuous Performance Test | | | |
| Vigilance level | –0.22 | –0.09 | 0.05 |
| Vigilance decrement | –0.17 | –0.21 | –0.14 |
| Span of Apprehension | | | |
| Number correct | 0.28 | 0.26 | 0.12 |
| Latency | –0.15 | –0.11 | –0.03 |
| Pin Test | | | |
| Right hand | 0.64[c] | 0.51[d] | 0.24 |
| Left hand | 0.47[e] | 0.41[e] | 0.21 |

[a] Multiple $R^2$ values were 0.50 for condition 1 and 0.38 for condition 4.

[b] The partial correlation is between the information processing measures and the number correct in condition 4 after partialling out the number correct from condition 1.

[c] $p<0.001$.

[d] $p<0.01$.

[e] $p<0.05$.

tion ($F=2.99$, $df=3, 189$, $p<0.05$). Comparisons were made separately for each group. Similar to the results for perseverative errors, both groups differed from baseline in conditions 3 and 4 ($p<0.0003$ after Bonferroni correction) but not in condition 2. The significant interaction can be attributed to a significantly larger difference between groups at condition 4 than at condition 1 ($F=5.8$, $df=1, 64$, $p<0.02$), suggesting that the psychiatric control subjects might have showed more improvement during the final condition.

### *Correlates of Test Performance*

Pearson product-moment correlation coefficients were obtained between each of the six information processing measures and the number correct (table 2). The three measures from the Wisconsin Card Sorting Test were highly intercorrelated, and the number correct was chosen because it shared the most variance with the other two measures. We looked at the number correct for condition 1 and condition 4 and at the partial correlation with condition 4 controlling for condition 1, which gives an indication of the amount of change during the session. The measures from the Degraded-Stimulus Continuous Performance Test or the Span of Apprehension did not show significant correlations with the Wisconsin Card Sorting Test variables for condition 1 or for improvement across conditions. However, both the left- and right-hand scores from the Pin Test showed moderate correlations with the number correct. This relationship seemed to generalize to other Wisconsin Card Sorting Test variables because the Pin Test also showed moderate correlations with categories ($r=0.61$ for right hand, $r=0.48$ for left hand) and perseverative errors ($r=-0.47$ for right hand, $r=-0.34$ for left hand) for condition 1.

The means and standard deviations of the BPRS indexes for these 27 schizophrenic patients were 10.1±4.1 for the psychotic index, 5.8±2.6 for depression, and 8.0±4.0 for withdrawal/retardation. Correlation coefficients were obtained between each of the three BPRS indexes and the Wisconsin Card Sorting Test measures. These correlations ranged from –0.03 to 0.17, and none reached significance.

## DISCUSSION

The present results suggest that the performance deficits of schizophrenic patients on the Wisconsin Card Sorting Test can be remediated by a combination of reinforcement and detailed instructions. Although the psychiatric control subjects performed somewhat better than the schizophrenic patients, the effects of the interventions were comparable. In the light of previous studies by Goldberg et al. (10) and Bellack et al. (12), our results suggest that even patients with chronic schizophrenia can show short-term benefits from training. Although direct comparisons are difficult, the current study group is probably much closer to the study group of chronically ill patients of Goldberg et al. than the study group of acutely ill patients of Bellack et al. The Bellack et al. subjects were comparable to our subjects in their scores on the psychotic items of the BPRS (average of 3.3 versus 3.4), but their subjects had been hospitalized for an average of 20 days before testing while ours were hospitalized for an average of 9.7 months before testing.

The use of reinforcement alone did not significantly improve Wisconsin Card Sorting Test performance. Perhaps the amount of reinforcement was not sufficient (2 cents per response). Bellack et al. (12) reinforced 5 cents per response but did not notice a beneficial effect. However, Summerfelt et al. (14) reported improved performance when they gave schizophrenic patients a stake ($7.50) and then paid them 10 cents for each correct response and penalized them 5 cents for each wrong response. These results indicate that some subjects might benefit from monetary incentives that are larger than were used in the present study.

The introduction of detailed instructions improved performance, and this improvement was largely maintained shortly after the withdrawal of instructions. Although it was not specifically tested, the continuation of monetary reinforcement might have accounted for the maintenance of improved performance. It is entirely possible that the present study group (like that of Goldberg et al.) would have returned to baseline levels of performance without the reinforcement, especially considering that our patients initially performed worse than did those of Goldberg et al. (e.g., our patients completed 1.5 categories and their patients completed 3 categories in the first 128 trials). It would be valuable to follow up these findings with a between-group design that could directly compare the impact of reinforcement with that of instructions.

When applied to rehabilitation efforts, our results suggest the importance of combining motivational with specific instructional factors for training in problem solving. In terms of neuroanatomy, the results might indicate that effective remediation requires involvement of both prefrontal and limbic regions.

A fairly striking correlation was observed between the Wisconsin Card Sorting Test variables and Pin Test results in the first and last conditions. This association deserves closer scrutiny. Perhaps neuromotor sequencing might yield a more basic measure of activation that operates at a precognitive stage and underlies higher-level processing.

In contrast to a recent study by Braff et al. (13), negative symptoms were not found to be associated with Wisconsin Card Sorting Test performance. Compared with the study group of Braff et al., our schizophrenic patients had substantially more impairment on the Wisconsin Card Sorting Test, had more chronic illness, and may have had more deficit symptoms. Hence, the range of our analyses might have been comparatively restricted.

For future research in this area, investigators are encouraged to look both "inward" (to identify the nature of Wisconsin Card Sorting Test deficits) and "outward" (to see if these deficits correspond to adaptive functioning). The Wisconsin Card Sorting Test requires subjects to attain a concept, maintain the concept, and switch the concept. Much interest has been devoted to problems in switching the concept: perseverative errors are often chosen as the dependent measure. Although our subjects showed considerable perseverative errors, 54% could not attain a single category in the first 64 trials. Hence, our subjects also had problems in attaining and/or maintaining concepts.

The generalizability of Wisconsin Card Sorting Test performance can be addressed empirically. For example, successful learning on the Wisconsin Card Sorting Test with instruction and reinforcement might be associated with success in skills training procedures. We had previously hoped to identify groups of learners and nonlearners based on their improvement on the Wisconsin Card Sorting Test (23). However, the improvement scores showed a negatively skewed distribution without a point of rarity and did not support the notion of distinct subgroups. Nonetheless, initial screening of problem-solving capacity might yield an empirical basis for selecting patients who are most likely to benefit from social and behavioral rehabilitation programs.

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# Clozapine-Induced Weight Gain: Prevalence and Clinical Relevance

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*Objective: The aim of this study was to determine the prevalence and clinical relevance of weight gain during clozapine treatment. Previous reports indicated clinically significant weight gain in 13% to 85% of patients and an average gain of 9.0 to 24.7 lb. Method: Twenty-one state hospital patients with treatment-resistant schizophrenia or schizoaffective disorder were weighed weekly for 12 weeks before clozapine treatment and during the first 16 weeks of treatment. Psychiatric symptoms were rated with a modified version of the Brief Psychiatric Rating Scale (BPRS). Results: The mean weight gain for the entire group was 13.9 lb, or 8.9% of body weight. During the 16 weeks of clozapine treatment, 38% of the patients experienced marked weight gains and 29% had moderate weight gains. The improvements in BPRS total score and composite negative symptom score were significantly greater for the eight patients with marked weight gains than for the other 13 patients. Conclusions: Clozapine's propensity to induce weight gain may relate to the drug's efficacy and/or its unique neuropharmacologic effects. Increased attention to this phenomenon is important because of the morbidity associated with obesity.*

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Many patients with schizophrenia suffer from obesity (1–3), which is associated with excessive rates of morbidity and mortality (4). Institutionalization, lack of exercise, poor diet, and misperception of satiety have been linked to the high prevalence of obesity in schizophrenia (2, 3, 5, 6). Studies have shown that weight changes relate to the severity of psychosis (3) and that weight gain is associated with clinical improvement (3, 7–9).

Chlorpromazine treatment is frequently associated with weight gain (3, 4, 8–12). Other standard antipsychotic drugs associated with weight gain include perphenazine and clopenthixol (4), fluphenazine (12–16), and thiothixene, haloperidol, and thioridazine (12). In contrast, molindone (10, 17) and loxapine (12) appear to cause weight loss. Amdisen (4) found that patients treated with antipsychotic agents reached weights associated with mortality rates 35% to 100% higher than normal. Singh et al. (7) showed that perphenazine increases appetite and caloric intake and perhaps increases metabolic efficiency and alters the body weight set point.

Clozapine is an atypical antipsychotic considered to have superior efficacy for patients with treatment-resistant psychosis (18). The drug's manufacturer noted a 1% prevalence of weight gain among 13,000 patients (19). However, as early as 1975 Norris and Israelstam (20) reported dramatic clozapine-induced weight gain in a group of 13 hospitalized adolescents with behavioral problems or acute schizophrenia. Nine of these patients "experienced an enormous increase in appetite," and four patients gained 22–44 lb during the first 2 months of treatment. Since then, various studies (21–27) have associated weight gain with clozapine treatment in 13% to 85% of patients, and the average weight gain was 9.0 to 24.7 lb. This wide range of reported weight gains stems in part from methodological differences among studies. For example, whether weight fluctuations were assessed during medication withdrawal is unclear in most reports. Also, other clinical or neurobiological factors correlating with weight changes were not accounted for in these patients.

During the preclinical trials of clozapine, we noted that many patients gained weight early in treatment

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(28). Because of the wide variance in the amounts of weight gained in previous studies and the discrepancy between these findings and the drug company's data, we examined the prevalence and magnitude of clozapine-induced weight gain, the clinical correlates of this problem, and the neurobiological factors that might explain this phenomenon.

**TABLE 1. Individual Weight Changes in Patients Receiving Clozapine**

| Patient | Sex | Weight (lb)<br>Before Clozapine | Weight (lb)<br>Week 16 | Change<br>Pounds | Change<br>% |
|---|---|---|---|---|---|
| Marked weight gain | | | | | |
| 1 | M | 158.0 | 197.0 | +39.0 | 24.7 |
| 2 | M | 194.0 | 239.0 | +45.0 | 23.2 |
| 3 | F | 148.0 | 178.5 | +30.5 | 20.6 |
| 4 | M | 152.0 | 179.0 | +27.0 | 17.0 |
| 5 | M | 161.0 | 188.0 | +27.0 | 16.8 |
| 6 | F | 120.0 | 140.0 | +20.0 | 16.7 |
| 7 | M | 147.0 | 170.0 | +23.0 | 15.6 |
| 8 | F | 155.0 | 174.0 | +19.0 | 12.3 |
| Moderate weight gain | | | | | |
| 9 | M | 119.0 | 130.0 | +11.0 | 9.2 |
| 10 | M | 183.3 | 196.5 | +13.2 | 7.2 |
| 11 | M | 153.5 | 164.0 | +10.5 | 6.8 |
| 12 | F | 135.0 | 144.0 | +9.0 | 6.7 |
| 13 | F | 170.0 | 180.0 | +10.0 | 5.8 |
| 14 | M | 155.0 | 163.5 | +8.5 | 5.5 |
| Mild/minimal weight gain | | | | | |
| 15 | M | 116.0 | 121.0 | +5.0 | 4.3 |
| 16 | M | 203.5 | 210.5 | +7.0 | 3.4 |
| 17 | F | 178.5 | 182.0 | +3.5 | 1.9 |
| 18 | M | 172.8 | 173.0 | +0.2 | 0.1 |
| Weight loss | | | | | |
| 19 | F | 131.0 | 128.0 | –3.0 | 2.3 |
| 20 | F | 111.5 | 107.5 | –4.0 | 3.6 |
| 21 | M | 201.3 | 191.0 | –10.3 | 5.1 |

## METHOD

### *Subjects and Procedure*

We studied 21 patients at a 600-bed state psychiatric facility. The subjects were 13 men and eight women, and their mean age was 32.6 years (range=19–47). The inclusionary criteria were a diagnosis of schizophrenia or schizoaffective disorder (*DSM-III-R*) and one of the following: 1) lack of response to adequate trials of several standard antipsychotic drugs, 2) intolerable side effects of those drugs, or 3) tardive dyskinesia. The exclusionary criteria were 1) a history of drug-induced agranulocytosis, 2) bone marrow abnormalities, or 3) a primary seizure disorder.

Treatment with carbamazepine and depot neuroleptic agents was stopped 2 weeks before the beginning of clozapine treatment. Standard antipsychotic and anticholinergic drugs were tapered over 1–4 weeks; the drug-free period was 24 to 48 hours. We increased the clozapine dose from 25 to 125 mg/week as tolerated and titrated the dose until a therapeutic response was achieved. We weighed the patients weekly with standard (counter-weight) hospital scales during the 12 weeks before and 16 weeks after the beginning of clozapine treatment, and ideal weight was based on established formulae (29).

We chose a modified version of the Brief Psychiatric Rating Scale (BPRS) to rate symptoms (30). A trained rater used a semistructured interview format to interview the patient and then consulted with other staff members and reviewed the patient's record before deriving a BPRS score. All ratings related to the patient's functioning during the prior week. The intraclass correlation coefficient for BPRS ratings of 13 videotaped interviews was 0.77 for eight trained multidisciplinary staff members.

### *Statistical Analyses*

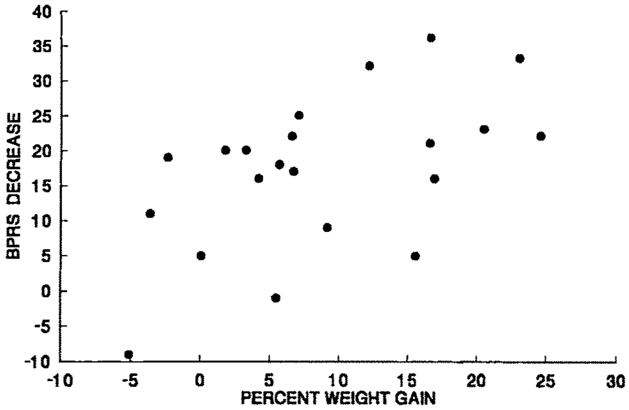
We conducted our statistical analyses in three phases. First, we compared the patients' weekly weights during the 12-week baseline period to the weights in the first 12 weeks of clozapine treatment, both as a group and individually, to assess whether a net weight gain was evident after conversion from standard neuroleptics to clozapine. We evaluated pre-post changes in weight gain using two-tailed, paired t tests. All remaining analyses focused on the weight changes from the start of clozapine treatment to the 16th week of treatment. We divided the patients into two groups on the basis of amount of weight gained and determined group differences in age, gender, pretreatment deviation from ideal body weight, and amount of weight change during tapering of standard antipsychotics. Third, we explored the clinical aspects of weight gain by comparing group differences in concurrent treatment with lithium and in psychiatric symptom ratings, using BPRS total scores and composite positive and negative symptom scores (18). Where appropriate, we used two-tailed, unpaired t tests and chi-square analyses and employed Bonferroni corrections to adjust the type I error rate in each of the three sets of analyses to guide our interpretation of statistical significance.

## RESULTS

As a group, the patients weighed significantly more during the first 12 weeks of clozapine treatment than during the preceding 12 weeks ($t=2.86$, $df=20$, $p<0.01$). When the patients were examined individually, it was found that 13 (62%) experienced significant increases in weight (Bonferroni correction, $p<0.05$). Seven (33%) of the patients lost weight during the tapering of standard antipsychotics, but the absolute weight change across patients was significantly less during the baseline period (mean= –0.44 lb) than during the first 12 weeks of clozapine treatment (mean=+13.8 lb) ($t=4.05$, $df=20$, $p<0.001$).

Table 1 presents each patient's weight at the onset of clozapine treatment and the weight at the 16th week of treatment. Eight patients experienced marked weight gains (greater than 10% increase), six had moderate

**FIGURE 1. Correlation Between Decrease in Total BPRS Score and Percentage of Weight Gained During 16 Weeks of Clozapine Treatment in 21 Patients[a]**



[a] r=0.54, df=19, p=0.01.

weight gains (5%–10% increase), four had mild to minimal weight gains (less than 5% increase), and three patients lost weight. Across all patients, the mean weight gain was 13.9 lb, or 8.9% of baseline body weight. Weight gain was particularly evident during the second half of the 16-week clozapine trial, as the doses reached therapeutic levels.

On the basis of the distribution of patients, we made a conservative decision to compare the eight patients who experienced marked weight gains (mean=28.8 lb) with the other 13 patients (mean gain=5.4 lb). There were no group differences in age, gender, deviation from ideal weight at the start of the drug trial, or amount of weight change during tapering of standard antipsychotics. Although the difference was not statistically significant, the mean pretreatment dose of standard neuroleptics, in chlorpromazine equivalents, was higher in the patients with marked weight gains (41.4 mg/kg, range=1.3–111.5) than in those who gained less weight (24.4 mg/kg, range=4.7–49.7). At 16 weeks there was no difference between groups in clozapine dose. The group of patients concurrently treated with lithium tended not to gain weight (Fisher's exact test, p<0.18); only two (20%) of these 10 patients experienced marked weight gains while taking lithium, whereas six (55%) of the 11 patients not treated with lithium had marked weight gains.

As indicated in figure 1, decrease in total BPRS score showed a significant positive correlation with percentage of weight gained. The patients who gained at least 10% of their body weight showed a significantly greater decrease in total BPRS score (mean=23.5) than the patients with less weight change (mean=13.3) (t=2.29, df=20, p<0.03). When we analyzed decreases in composite positive and negative symptom subscale scores separately, we found that the two groups' negative symptom scores were significantly different (t=2.61, df=20, p<0.02). Those with marked weight gains showed an average decrease of 6.0 on the negative symptom subscale, and those with less weight change showed an average decrease of 2.5.

In a second set of analyses we recalculated BPRS scores to reflect presence or absence of symptoms (no score=0, any score=1). These analyses corroborated the previous finding that a significant relationship existed between improvement and weight gain. Not only was there a significant difference between groups in the number of negative symptoms (t=2.58, df=20, p<0.02), but the number of positive symptoms also differed between groups (t=2.23, df=20, p<0.04). The subjects with marked weight gains showed an average reduction of 1.12 positive and 1.62 negative symptoms, compared with average reductions of 0.23 positive and 0.46 negative symptoms for those with less weight change.

## DISCUSSION

We found that 62% of patients weighed significantly more during the first 12 weeks of clozapine treatment than during the 12-week baseline. Although one-third of our patients lost weight during the tapering of standard antipsychotics before clozapine treatment, the weight loss during tapering was of significantly less magnitude than the weight gain during clozapine treatment. Also, there was no baseline weight difference between those who did and did not gain weight during clozapine treatment. To focus on true weight gain due to clozapine treatment we compared the absolute weight at the start of clozapine treatment to the weight at week 16 of treatment.

Fourteen (67%) of the 21 patients gained more than 5% of their baseline body weights. Previous reports addressing clozapine-induced weight gain indicated that 13% to 85% of patients experience this side effect (20–25, 27). Weight gains associated with standard antipsychotic drug treatments range from 14.5% to 80.0% (4, 7, 13, 14). Among our patients, clozapine was associated with a mean weight gain of 13.9 lb during the 16 weeks of treatment; previous studies showed an average gain of 9.0 to 24.7 lb over variable lengths of clozapine treatment (21, 23, 26, 27). In contrast, weight gains associated with standard antipsychotic drugs range between 3.4 and 9.0 lb over 12 weeks (8, 12).

A critical examination of this study requires attention to a number of clinical variables. There was no change in the patients' diets or access to food during this study, although we did start nutritional education once we noted weight gain. Several patients did complain of an inability to suppress appetite after a full meal, suggesting a change in satiety perception. Clozapine is frequently sedating, but we found that psychomotor retardation improved more in the patients with marked weight gains than in those who gained less weight. The mean chlorpromazine-equivalent dose was significantly lower during clozapine treatment than during the preceding treatment with standard antipsychotic agents. If there is a correlation between dose and weight gain, as one author has suggested (4), we should have noted weight loss during this study.

We noted a significant correlation between weight gain and improvement in total BPRS score. There also was greater improvement in the composite negative symptom score in the patients with marked weight gains. Reports do indicate that during treatment with standard antipsychotic drugs weight gain correlates with a decrease in psychosis (3, 7–9), although some authors disagree (4, 5). Alternatively, weight gain may be due to the psychotropic's effect on CNS mechanisms (31).

Characteristic neurotransmitter and neuroendocrine effects of antipsychotic agents could explain differences in their propensity to induce changes in weight and appetite regulation (32). For example, clozapine's ability to alter plasma cortisol concentration (33, 34), its adrenolytic effects (which have been attributed to clozapine-induced hyperphagia in rats [35]), and its unique $D_1$ and $D_2$ neurotransmitter effects (36–38) could be important factors in its induction of weight gain. Clozapine's potent serotonin antagonism (33) may be important, because serotonin agonists suppress appetite (39, 40), and other psychotropic drugs that either antagonize or down-regulate serotonin receptors, such as chlorpromazine (41) and fluphenazine (15), are more likely to stimulate carbohydrate craving and weight gain (31). We observed that lithium, which influences serotonin transmission (42), tended to protect patients from weight gain.

We have continued to follow clozapine-induced weight gain in this group of patients and have found that the rate of weight gain was greatest during the first 16 weeks of treatment and that the rate of weight gain decreased with time. At this point, one cannot absolutely rule out a variety of biological variables in explaining the etiology of weight gain. Nonetheless, we have shown an association between clozapine-induced weight gain and clinical improvement in patients who were previously treatment resistant. Perhaps clozapine would be useful in the treatment of end-stage anorexia nervosa, given that this illness is often treatment resistant and quasipsychotic. In the chronically mentally ill, however, increased attention to drug-induced weight gain is important because of the greater susceptibility to weight gain associated with clozapine and concomitant excessive morbidity and mortality.

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# Seasonal Patterns of Bulimia Nervosa

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*Objective: The aim of this research was to determine whether a seasonal pattern to symptoms of bulimia nervosa could be identified. Method: In study 1, seasonal patterns of binge-purge frequency and mood were compared between 31 patients with bulimia nervosa and 31 age-matched normal comparison subjects, using a modified (to include binge and purge items) version of the Seasonal Pattern Assessment Questionnaire. Study 2 involved a cross-sectional examination of binge and purge frequency and of depressive symptoms in 197 patients with bulimia nervosa assessed at various months of the year over a 4-year period. Results: In both the retrospective and cross-sectional studies, binge behavior was found to be highly associated with photoperiod. According to the modified Seasonal Pattern Assessment Questionnaire, purging behavior and mood also varied seasonally among patients with bulimia nervosa. However, purging behavior and severity of depression did not appear to be related to photoperiod in the cross-sectional study. The rate of seasonal affective disorder (syndromal and subsyndromal) defined by the Seasonal Pattern Assessment Questionnaire was higher among the bulimic group than the comparison subjects, but not as high as has been reported for depression in bulimia nervosa. Conclusions: The results strongly support the interpretation that symptoms of bulimia nervosa primarily associated with food intake patterns are influenced by seasonal variation, and this effect may be mediated by light availability.*

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To date, seasonal patterns in bulimia nervosa have not been well documented. Evidence to suggest that bulimia nervosa is sensitive to seasonal patterns is indirect and arises from a single study that examined symptoms of seasonal affective disorder among patients with bulimia nervosa. Fonari et al. (1) found that patients with bulimia nervosa reported feeling worse and eating more in the winter than at other times of the year. Although this seasonal effect was greater for bulimic patients than for normal control subjects, it was not equivalent to the effects reported by patients with seasonal affective disorder (1). Rosenthal et al. (2) have suggested that binge eating in bulimia nervosa may follow a seasonal pattern, since patients with bulimia nervosa and patients with seasonal affective disorder share common symptoms, including carbohydrate craving and binge eating (3, 4).

The cardinal symptom of bulimia nervosa is defined in *DSM-III-R* as recurrent episodes of binge eating. Depressed mood is listed as a common associated feature. The cardinal feature of seasonal affective disorder, according to *DSM-III-R*, is an affective disturbance with recurrent onset in a particular 60-day period of the year. Two of the most common associated features of seasonal affective disorder are increased appetite and carbohydrate craving (2–4). This is in contrast to nonseasonal depression, which is typically associated with loss of appetite and is less frequently associated with carbohydrate craving than is seasonal affective disorder (5). In addition to sharing similar affective and appetitive symptoms, bulimia nervosa and seasonal affective disorder share the feature of gender specificity. Bulimia occurs predominantly in females (over 90%) (6), as does seasonal affective disorder (over 80%) (2–4). It has been demonstrated that the symptoms of both bulimia nervosa and seasonal affective disorder respond to increased central serotonergic activation. Both fenfluramine and fluoxetine have been shown to be effective in treating bulimia nervosa (7, 8), and fenfluramine has also been reported to be effective in seasonal affective disorder (9, 10).

The present study examined seasonal patterns of

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binge eating, purging, and mood in bulimia nervosa. Previous studies of seasonal effects on mood have relied on the Seasonal Pattern Assessment Questionnaire (3), which has been demonstrated to be highly sensitive to seasonal effects (11). However, the questionnaire relies on retrospective self-report and may be biased by subject expectation. To address this weakness, the present study incorporated two separate methodological approaches. The first is in keeping with previous studies, comparing the results of the Seasonal Pattern Assessment Questionnaire among a group of patients with bulimia nervosa and a normal comparison group. The normal comparison group is included in order to determine whether the questionnaire reports of seasonal variation in mood exceed those of a group without eating disorders and of comparable age and sex. The second study is a cross-sectional examination of bulimic and depressive symptoms reported by patients with bulimia nervosa as part of their first clinical intake assessment during different months of the year.

## STUDY 1

### *Method*

*Subjects.* Thirty-one volunteer subjects who met *DSM-III-R* criteria for bulimia nervosa were selected from a group of 58 patients consecutively referred to the eating disorders clinic of a large (900-bed) urban general hospital. Excluded were referred patients who did not meet *DSM-III-R* criteria for bulimia nervosa. All subjects were women and of normal weight. Three had a lifetime history of anorexia nervosa. They were not receiving treatment for their eating disorder at the time of the study. The diagnoses of bulimia nervosa and anorexia nervosa were based on 1) the subjects' responses to the bulimia and anorexia nervosa sections of the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (12) and 2) positive diagnosis based on psychiatric interview. The diagnoses were further confirmed by subjects' responses to the Diagnostic Schedule for Eating Disorders (13) and to the Eating Disorders Inventory (14). The diagnosis of depression was based on subjects' responses to the depression section of the DIS.

Thirty-one normal comparison subjects, comparable in age to the bulimic subjects, were selected from a volunteer group of 61 female university students and 36 female hospital employees. The only criteria used in selecting the comparison group were that 1) they volunteered, 2) they had no history of an eating disorder, according to their responses to the bulimia nervosa and anorexia nervosa sections of the DIS (12), and 3) as a group, their age was comparable in distribution and range to that of the bulimic subjects. All volunteer subjects signed informed consent forms, and the entire protocol was approved by the Research Ethics Committees of the Ottawa Civic Hospital and Carleton University.

*Procedure.* Patients attending the eating disorders clinic routinely undergo a comprehensive intake that includes the DIS, a psychiatric interview, and complete psychological assessment. Each subject in the present study (patients and comparison subjects) completed a modified version of the Seasonal Pattern Assessment Questionnaire (3). The questionnaire has been demonstrated to have acceptable test-retest reliability and discriminant validity (11). It is divided into seven sections: 1) demographics, 2) degree of change in seasonal affective disorder symptoms, 3) months most affected, 4) climatic changes, 5) changes in weight and food preference, 6) sleep, and 7) extent to which seasonal affective disorder changes are problematic. Section 2 presents six 5-point scales (0="no change," 4="extremely marked change") measuring length of sleep, social activity, mood, weight, appetite, and energy level. The first criterion for seasonal affective disorder is that the sum of the subject's scores for each of these items is greater than 10. The second criterion is a report, in the seventh section of the questionnaire, of "moderate" to "disabling" problems with seasonal changes. Subsyndromal seasonal affective disorder was identified by a seasonality score of 10 with mild or less seasonal problems, or a seasonality score of 8 or 9 with at least mild problems with seasonal changes.

The third section of the Seasonal Pattern Assessment Questionnaire asks subjects to indicate the months in which they are most likely to experience certain behaviors, by making a yes/no response for each month, for each behavioral item. The items include "feel best," "feel worst," "gain most weight," "lose most weight," "socialize most," "socialize least," "sleep most," "sleep least," "eat most" and "eat least." For the purpose of this study, the questionnaire form was modified so that three-letter monthly abbreviations were displayed immediately above the recording location for each month, for every item, rather than a single letter at the bottom of the column for all items, as on the original form. The modified questionnaire used the same format to assess the months in which the subject was most likely to binge and to purge.

Meteorological data included monthly means for hours of bright sunshine, global solar radiation (measured in megajoules per square meter of energy striking a horizontal surface), temperature, and precipitation in Ottawa, averaged separately for each month for the years 1951 to 1980. These data were obtained from the 1989 Annual Meteorological Summary published by Environment Canada for Ottawa (15). Data on photoperiod were obtained from the Herzberg Institute of Astrophysics of the National Research Council of Canada, using formulae published elsewhere (16). Ottawa is situated at 45°19'N latitude, 75°40'W longitude. The city has a marked continental climate with relatively large temperature variations throughout the year. Average temperature extremes range from –15 °C during January to 26 °C in July. Over the year, there is an average of 2,008 hours of bright sunshine. July normally has the greatest number of sunny hours (274 hours) and December the least (79 hours) (15).

**TABLE 1. Characteristics of the Subjects in Study 1 and Study 2 of the Seasonal Patterns of Bulimia Nervosa**

| | Study 1 Subjects | | | | | | | | Study 2 Bulimic Subjects (N=197) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bulimic (N=31) | | | | Control (N=31) | | | | | | | |
| Item | Mean | SD | N | % | Mean | SD | N | % | Mean | SD | N | % |
| Age (years) | 24.6 | 6.0 | — | — | 24.7 | 6.2 | — | — | 26.0 | 7.4 | — | — |
| Socioeconomic status[a] | 2.7 | 1.5 | — | — | 2.3 | 1.4 | — | — | 2.5 | 0.9 | — | — |
| Weight (lb) | 144.1 | 48.1 | — | — | 126.9 | 16.3 | — | — | 133.8 | 31.3 | — | — |
| Height (in) | 64.8 | 2.2 | — | — | 64.7 | 2.1 | — | — | 64.5 | 2.7 | — | — |
| Binge episodes/week | 8.7 | 5.9 | — | — | 0.0 | 0.0 | — | — | 7.3 | 7.4 | — | — |
| Purge episodes/week | 11.2 | 12.0 | — | — | 0.0 | 0.0 | — | — | 6.5 | 7.7 | — | — |
| Single marital status | — | — | 29 | 93.5 | — | — | 21 | 66.7 | — | — | 139 | 70.6 |
| DIS major depression | — | — | 15 | 48.4 | — | — | — | — | — | — | 122 | 61.9 |

[a] Hollingshead and Redlich (17).

*Statistical analysis.* The analysis of variance (ANOVA) employed one between-subjects factor (group: bulimic versus comparison group) and one within-subjects factor (month: January through December). Dependent measures included the self-reports of months when the subjects were most likely to binge, purge, and experience the 10 other behaviors and feelings itemized in section 3 of the modified Seasonal Pattern Assessment Questionnaire. Significant ANOVA results were followed with univariate tests of differences between the two groups for each month.

A multivariate ANOVA was used to test the significance of differences between the bulimia nervosa and normal comparison groups in response to items in section 2 of the Seasonal Pattern Assessment Questionnaire that assess the degree to which the respondent is affected by seasonal change in six areas. A significant multivariate effect was to be followed with six univariate ANOVAs.

Photoperiod was converted to "dark hours" (24 hours minus the average photoperiod for each month) in order to enhance the graphical display of the association between bulimic symptoms and photoperiod. The dark hours included twilight hours at dusk and dawn. Pearson correlations were calculated between 1) the meteorological variables (dark hours, hours of bright sunshine, global solar radiation, temperature, and precipitation) averaged for each month and 2) the proportion of patients who reported on the Seasonal Pattern Assessment Questionnaire a given month as the month in which they were most likely to binge, purge, or feel worst. These correlations were based on group results, yielding a total of 12 (one for each month) for each correlation. Correlations were calculated separately for the bulimia nervosa group and the normal comparison group results.

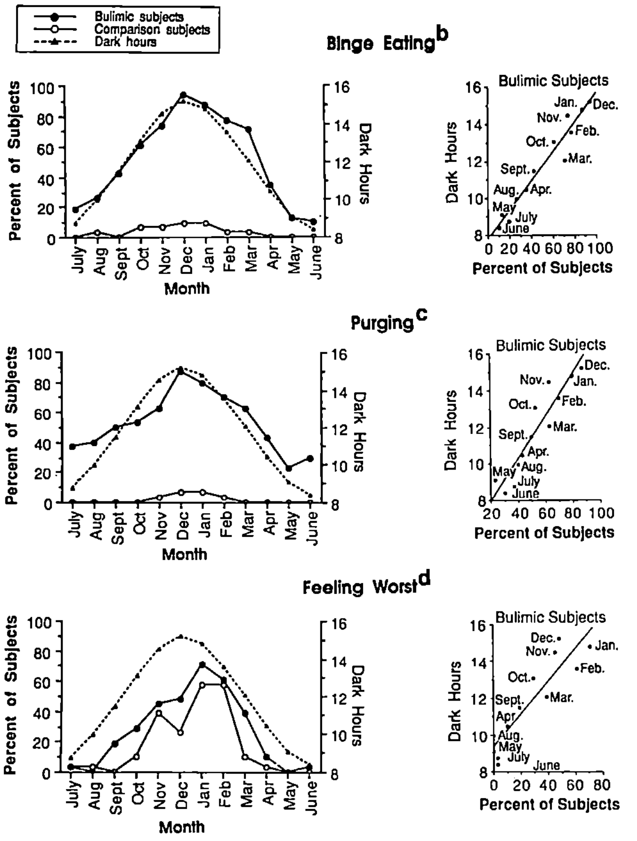
### *Results*

*Group characteristics.* Characteristics of the bulimic and comparison groups appear in table 1. Both groups averaged 24 years of age and were of equivalent socioeconomic status. Fewer of the bulimic patients were married, and the bulimic patients tended to report a higher body weight, but neither of these differences attained statistical significance. The bulimic group binged an average of 8.7 times per week and purged an average of 11.2 times per week.

Among the bulimic group, 11 (35.5%) of the 31 patients met the criteria of the Seasonal Pattern Assessment Questionnaire for either seasonal affective disorder (eight patients) or subsyndromal seasonal affective disorder (three patients). This frequency was significantly higher ($\chi^2$=6.23, df=1, p<0.02) than the two (6.5%) (one syndromal, one subsyndromal) reported in the comparison group. Among the bulimic patients, 15 (48.4%) reported symptoms of a lifetime history of major depressive disorder. There was no association between frequency of seasonal affective disorder or subsyndromal seasonal affective disorder, as defined by the questionnaire, and the frequency of major depressive disorder; of the 15 depressed bulimic patients, five (33%) met criteria for seasonal affective disorder or subsyndromal seasonal affective disorder, while six (37.5%) of the nondepressed bulimic patients met these criteria.

*Meteorological measures.* The meteorological measures of dark hours, hours of bright sunshine, global solar radiation, and temperature per month were highly intercorrelated. Dark hours were significantly negatively associated with global solar radiation (r=–0.99, df=12, p<0.001), hours of bright sunshine (r=–0.97, df=12, p<0.001), and temperature (r=–0.86, df=12, p<0.001) but not precipitation (r=–0.32, df=12, n.s.). Hours of bright sunshine were correlated with global solar radiation (r=0.97, df=12, p<0.001) and temperature (r=0.87, df=12, p<0.001) but not precipitation (r=0.40, df=12, n.s.). Global solar radiation was correlated with temperature (r=0.81, df=12, p<0.001) but not precipitation (r=0.29, df=12, n.s.). Precipitation was associated with temperature (r=0.62, df=12, p<0.05). Precipitation did not exhibit significant associations with bulimic symptoms. Since the remaining meteorological measures were so highly intercorrelated (and each was significantly associated with bulimic symptoms), their independent effects on the behavioral measures could not be adequately assessed. The measure of dark hours was therefore employed as a proxy variable for a class of measures representing availability of light and temperature. The measure of dark hours was selected because it correlated most highly with

**FIGURE 1. Seasonal Variations[a] in Binge Eating, Purging, and Feeling Worst Among 31 Bulimic and 31 Comparison Subjects**



[a]Binge eating, purging, and feeling worst were determined according to the modified Seasonal Pattern Assessment Questionnaire. Number of dark hours was defined as 24 hours minus the average photoperiod for each month.

[b]A significant group effect (F=103.99, df=1, 60, p<0.001), month effect (F=9.91, df=11, 50, p<0.001), and Group by Month interaction (F=7.06, df=11, 50, p<0.001) were found. The correlation between number of dark hours and likelihood of binge eating was significant (r=0.97, df=12, p<0.001).

[c]A significant group effect (F=83.77, df=1, 60, p<0.001), month effect (F=3.99, df=11, 50, p<0.001), and Group by Month interaction (F=2.76, df=11, 50, p<0.007) were found. The correlation between number of dark hours and likelihood of purging was significant (r=0.94, df=12, p<0.001).

[d]A significant group effect (F=6.46, df=1, 60, p<0.02) and Group by Month interaction (F=2.50, df=11, 50, p<0.02) were found. The correlation between number of dark hours and likelihood of feeling worst was significant (r=0.92, df=12, p<0.001).

binge eating and purging and because photoperiod has been previously linked to seasonal changes in mood in seasonal affective disorder (18).

*Seasonality of bulimic symptoms.* Seasonal variations in binge eating, purging, and mood are presented in figure 1 for the bulimia nervosa and normal comparison groups. Also displayed are the dark hours for each month. As expected, the ANOVA revealed a significant group effect (F=103.99, df=1, 60, p<0.001) for binge eating (figure 1, top left). The post hoc multiple comparisons, with the Bonferroni correction, revealed that for every month except the summer months of May, June, July, and August, bulimic patients binged more frequently than those in the comparison group. There were also significant effects of month (F=9.91, df=11, 50, p<0.001) and Group by Month interaction (F=7.06, df=11, 50, p<0.001) on binge frequency. Examination of the interaction effect revealed that the monthly variation in binge eating was far stronger in the bulimic group than in the comparison group.

Effects on purging were similar. Because there was very little purging reported among the normal comparison group, the bulimia nervosa group reported a greater likelihood of purging across all months (F=83.77, df=1, 60, p<0.001) and, among the post hoc comparisons with the Bonferroni correction, for each individual month. Significant effects of month (F=3.99, df=11, 50, p<0.001) and the Group by Month interaction (F=2.76, df=11, 50, p<0.007) were also found. Not surprisingly, examination of the interaction revealed a far stronger monthly variation in purging for bulimic patients than for those in the comparison group.

The item from the Seasonal Pattern Assessment Questionnaire most frequently used to examine seasonal effects on mood is the item that addresses the time of the year when the subject "feels worst." In this case both the bulimia nervosa and normal comparison groups exhibited seasonal effects (figure 1, bottom left). The ANOVA indicated a significant group (bulimic versus comparison group) effect (F=6.46, df=1, 60, p<0.02) and a significant Group by Month interaction (F=2.50, df=11, 50, p<0.02). The results of the t tests indicated that while the bulimia nervosa group reported feeling worst more than did the normal comparison group, this difference did not achieve statistical significance for any particular month after the Bonferroni correction for multiple comparisons was applied.

*Meteorological effects on behavioral measures.* The influence of dark hours on the proportion of subjects who reported binge eating in each month is displayed in figure 1 (top right). Dark hours significantly predicted the proportion of subjects who reported binge eating in each month (r=0.97, df=12, p<0.001). A time series cross-correlation analysis (between binge eating and dark hours) was conducted at monthly lags of from 0 to 5 in order to evaluate 1) time delays and 2) periodicity of the association (table 2). The 0 lag correlation was highest, indicating that monthly changes in binge eating were best predicted by the dark hours within the current month (rather than previous months). The maximal reversal of the correlation was obtained at a lag of 5, indicating a 12-month cycle.

A similar pattern was observed for the correlation of photoperiod and purging (figure 1, middle right). In this case, the 0 lag correlation (r=0.94, df=12, p<0.001) was again the highest, and the maximal reversal of the correlation occurred at a lag of –5. Photoperiod also strongly predicted the likelihood of feeling worst each month. The 0 lag correlation (r=0.92, df=12, p<0.001) was also the highest, with the highest reversal at a lag of 4.

A quadratic equation significantly explained the monthly variation in photoperiod ($R^2$=0.90, df=12,

**TABLE 2. Cross-Correlation Analysis of Binge Eating, Purging, and Feeling Worst With Photoperiod Among the Subjects With Bulimia Nervosa in Study 1**

| | Lag (months)[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | –6 | –5 | –4 | –3 | –2 | –1 | 0 | 1 | 2 | 3 | 4 | 5 |
| Binge | –0.52 | –0.58 | –0.39 | 0.03 | 0.40 | 0.78 | 0.97 | 0.63 | 0.14 | –0.30 | –0.51 | –0.57 |
| Purge | –0.54 | –0.64 | –0.41 | 0.01 | 0.40 | 0.76 | 0.94 | 0.62 | 0.12 | –0.29 | –0.51 | –0.56 |
| Feel worst | –0.56 | –0.52 | –0.32 | 0.05 | 0.45 | 0.80 | 0.92 | 0.56 | 0.06 | –0.41 | –0.64 | –0.60 |

[a] The lag (in months) represents the number of months the photoperiod data are shifted when the correlations with self-report items are calculated. A lag of 0 means that the January photoperiod data are lined up with the January self-report item, February with February, etc., for all 12 months. A correlation at –1 month lag is the result of associating December photoperiod with January self reports, January with February, etc. This is repeated until all possible lagged correlations are obtained.

$p<0.001$), as well as in reported binge eating ($R^2=0.90$, df=12, $p<0.001$), purging ($R^2=80$, df=12, $p<0.01$), and mood ($R^2=0.77$, df=12, $p<0.01$) among the bulimia nervosa group, and in binge eating ($R^2=0.62$, df=12, $p<0.01$) and mood ($R^2=0.52$, df=12, $p<0.01$) among the normal comparison group.

*Seasonality of Seasonal Pattern Assessment Questionnaire behavioral measures.* ANOVAs revealed significant monthly variations (across both bulimic and comparison groups) for the remaining nine behavioral/emotional items listed in section 3 (months most affected) of the Seasonal Pattern Assessment Questionnaire. Both groups reported significant monthly fluctuations in their likelihood to eat most, eat least, socialize most, socialize least, gain weight, lose weight, sleep most, sleep least, and feel best (results for feel worst were reported earlier in this article). Bulimic patients were more likely than those in the comparison group to report being most likely to gain weight ($F=4.03$, df=1, 60, $p<0.05$) and most likely to eat most ($F=9.32$, df=1, 60, $p<0.003$) across months. There was also an effect of the interaction of group and month on reported likelihood of eating most; this effect was of marginal significance ($F=1.86$, df=11, 50, $p<0.07$). The only months during which bulimic patients were significantly more likely than those in the comparison group to report eating most (after the Bonferroni correction was applied) were November ($t=2.94$, df=60, $p<0.005$) and February ($t=4.39$, df=60, $p<0.001$). In both groups the highest proportion of subjects reported that they ate most in December (81% [N=25] of bulimic patients and 68% [N=21] of comparison subjects).

These results indicate that significant monthly patterns in weight fluctuation and eating were experienced by both bulimic patients and comparison subjects. Compared to the normal comparison group, the patients with bulimia nervosa reported greater seasonal increases in weight and eating during late fall and winter.

*Degree of change in Seasonal Pattern Assessment Questionnaire seasonal symptoms.* Multivariate ANOVAs revealed that bulimic patients reported a significantly stronger degree of seasonal change than did comparison subjects in the six symptoms addressed in section 2 (degree of change in seasonal affective disorder symptoms) of the questionnaire ($F=2.778$, df=6, 55, $p<0.02$). Post hoc univariate analyses that used the Bonferroni correction revealed that bulimic patients reported a stronger degree of seasonal change in sleep ($F=7.83$, df=1, 60, $p<0.007$), mood ($F=8.41$, df=1, 60, $p<0.005$), weight ($F=12.07$, df=1, 60, $p<0.001$), and energy ($F=7.90$, df=1, 60, $p<0.007$) than did the comparison group.

## STUDY 2

### *Method*

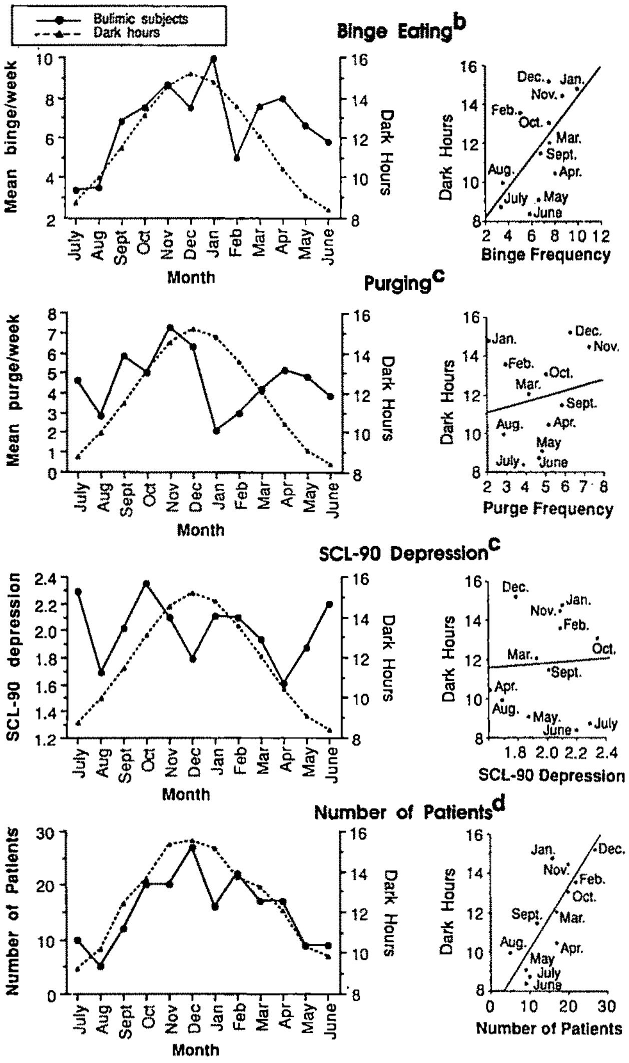
*Subjects.* The subjects in this study were 197 patients from the eating disorders clinic who met *DSM-III* criteria (182 patients) or *DSM-III-R* criteria (15 patients) for bulimia or bulimia nervosa. They were selected for this study, on the basis of this diagnosis, from 345 consecutively referred patients who were assessed between 1984 and 1988. Of the 197 subjects, 193 were women and four were men. The diagnosis of bulimia or bulimia nervosa was based on subjects' responses to the DIS (12) in the case of bulimia, or to the revised version of the DIS (DIS-R) in the case of bulimia nervosa. The diagnosis was confirmed by clinical interview and was supported by subjects' responses to the Eating Disorders Inventory (14) and Diagnostic Schedule for Eating Disorders (13).

*Procedure.* As part of the standard assessment procedure in the eating disorders clinic, subjects completed a self-report questionnaire regarding frequency of binge eating and vomiting in the previous week. They also completed the 90-item Symptom Checklist-Revised (SCL-90-R) (19), the Eating Disorders Inventory, Diagnostic Schedule for Eating Disorders, and either the DIS or DIS-R. Date of assessment and date of birth were recorded for every subject. Environmental data for mean monthly temperature, hours of bright sunshine, global solar radiation, and dark hours were gathered, as described in study 1. Again, because of very high intercorrelations, the measure of dark hours was used as the proxy variable representing temperature, global solar radiation, and hours of sunshine.

### *Results*

*Group characteristics.* The 197 bulimic subjects had a mean age of 26 years, an average weight of 134 lb, and an average height of 5 ft 4 in. They reported binge eating an average of 7.3 times per week, self-induced vomiting

FIGURE 2. Seasonal Variations[a] in Binge Eating, Purging, Depression, and Number of Patients Among 197 Bulimic Subjects



[a]Binge eating and purging were defined on the basis of patients' self-reports of symptom frequency. Depression was defined as the raw score obtained on the SCL-90 depression subscale. Number of dark hours was defined as 24 hours minus the average photoperiod for each month.

[b]Binge eating frequency was significantly correlated with number of dark hours ($r=0.63$, $df=12$, $p<0.03$).

[c]No significant correlation with dark hours was found.

[d]Number of new patients seen in the clinic who met *DSM-III* criteria for bulimia was correlated significantly with number of dark hours ($r=0.86$, $df=12$, $p<0.001$).

an average of 5.0 times per week, and an average of 6.5 total purge episodes (including laxative use) per week. Thirty-five percent (N=69) of the group met *DSM-III* criteria for recurrent major depression, while 61.9% (N=122) met criteria for a lifetime diagnosis of affective disorder (i.e., major depressive episode: 53.2% [N=65], dysthymic disorder: 27.1% [N=33], atypical bipolar disorder: 12.8% [N=16]). The average SCL-90-R depression score of 2.03 represented a T score of 69 based on norms for nonpatient women. A lifetime diagnosis of anorexia nervosa (according to subjects' responses to the DIS) was made for 7.5% of the subjects.

*Seasonality of symptoms.* Mean binge frequency reported by each subject at the time of the initial assessment was significantly correlated with dark hours in the month of the assessment ($r=0.63$, $N=12$, $p<0.03$) (figure 2, top left and right). However, mean purge frequency and mean SCL-90-R depression scores were not significantly related to the environmental variables of dark hours (figure 2), hours of bright sunshine, temperature, or global solar radiation. There were no significant relationships between month of birth and frequency of binge eating, frequency of purging, or depression score. The number of patients who met *DSM-III* criteria for bulimia, who presented to the clinic by month, correlated significantly with monthly dark hours ($r=0.86$, $N=12$, $p<0.001$) (figure 2, bottom). A quadratic equation significantly predicted binge frequency ($R^2=0.59$, $df=12$, $p<0.01$) but not purge frequency or SCL-90-R depression score. Nonetheless, binge frequency and purge frequency were significantly correlated ($r=0.67$, $df=196$, $0<0.001$).

## DISCUSSION

It has been reported that a large percentage of the population shows seasonal changes in mood, energy, and appetite and that among a subgroup, these symptoms are sufficiently severe in the winter months to be considered a seasonal affective disorder (3, 4, 19–21). The present study indicates that seasonal changes also have a strong influence in bulimia nervosa. Using methods similar to those employed in previous studies of normal subjects and patients with seasonal affective disorder, we found that the retrospective self-reports of patients with bulimia nervosa indicate a far greater perceived likelihood of binge eating and purging during the winter than summer months. In addition, a cross-sectional analysis of patients with bulimia nervosa who presented to a clinic specializing in eating disorders also indicates that actual binge frequency varies seasonally, with greater binge frequency during the winter.

It is striking that seasonal binge eating, as assessed by the modified Seasonal Pattern Assessment Questionnaire in the present study, exhibits a monthly curve that is almost identical to that obtained from plotting dark hours, or the inverted curve of photoperiod. The high correlation (0.97) between binge eating and dark hours reflected a stable linear relationship over the entire 12 months of the year. Similar high correlations have been reported between mood and photoperiod among patients with seasonal affective disorder (3, 22). In each case, the associations have been based on retrospective self-reports that used the Seasonal Pattern Assessment Questionnaire. We recognized that this method may elevate the association, for several reasons. First, there is the problem of correlated error inherent in an instrument like the Seasonal Pattern Assessment Questionnaire. With this method, assessment of a single month is not independent of other months, and a tendency to cluster monthly reports may artificially elevate the strength of the association. Second, individuals may recall greater seasonal variation than actually exists. Third, the data from the modified questionnaire are based on the percentage of individuals who report that a given month is one of the months in which they are most likely to binge eat, but the data do not reflect the frequency of binge eating. The cross-sectional data addressing binge frequency among bulimic patients assessed in the clinic during different months of the year are therefore important, since the results support the finding that monthly binge eating is strongly associated with shorter photoperiod (or more dark hours), even when data for each month are collected independently.

This effect also appears to be significant clinically, since the number of patients presenting to the clinic who meet *DSM-III* criteria for bulimia was also significantly associated with photoperiod. It is unlikely that this effect is the result of seasonal changes in referral frequency or staff vacations, since the clinic is booked to see four new patients per week year round and maintains a waiting list of at least 2 to 4 weeks throughout the year. The only exception to this rule is that the clinic typically closes for 1 week in December for Christmas, but that was a month in which a peak number of patients met *DSM-III* criteria for bulimia. Since the number of appointments available per week remains relatively stable year round, the seasonal variation in number of patients with bulimia nervosa appears to be due to the fact that fewer of those seen in the summer actually meet the criteria for the disorder. This may reflect a seasonal variation in severity of the disorder, as suggested by the binge frequency data, although we cannot rule out other possible explanations for a selective seasonal predisposition for patients with bulimia nervosa to attend a clinic.

Since photoperiod is so highly correlated with the other climatic and meteorological variables, the independent effect of these variables cannot be adequately estimated. Statistical techniques such as covariance are limited in this case. Photoperiod was therefore used as a proxy variable representing wide-ranging climatic and meteorological change throughout the year. It is reasonable to suggest, however, that photoperiod, or, more specifically, availability of light, is associated with these effects because seasonal symptoms in patients with seasonal affective disorder can be reversed by phototherapy (22, 23). It remains to be determined whether phototherapy is effective in bulimia nervosa, and we are currently investigating this. To date, at least one published case report suggests that it may be effective (24).

In the present study a higher percentage of patients with bulimia nervosa than of normal comparison subjects met Seasonal Pattern Assessment Questionnaire criteria for syndromal and subsyndromal seasonal affective disorder. The rate of seasonal affective disorder in bulimia nervosa did not, however, approach the rate reported for affective disorders in bulimia nervosa, which has been estimated to be as high as 70%–80% (25, 26). Furthermore, the depression typically reported in bulimia nervosa was not found to be associated with the syndromal and subsyndromal seasonal affective disorder reported by patients with bulimia nervosa in this study. The high levels of depression consistently reported in bulimia nervosa cannot be accounted for by seasonal affective disorder, according to the results of the present study. In fact, the results lend themselves to the interpretation that the seasonal effects on bulimic symptoms may be independent of the effects on depressive symptoms. Consistent with the observations of Fonari et al. (1), the present study found that patients with bulimia nervosa report greater seasonal variation in weight gain and eating than do normal comparison subjects. Differences in the seasonal effects on mood were less pronounced. The peak periods of low mood from November through February were no different for bulimic patients than for comparison subjects. When depressive symptoms were examined by using the SCL-90-R in a cross-sectional design, no seasonal effects were obtained. The SCL-90-R has been reported to be sensitive to changes in depression. It has been demonstrated to be highly sensitive to both neurovegetative and cognitive symptoms of depression (19), correctly classifies over 70% of women assessed for depression according to the Feighner criteria (27), and shows a high degree of sensitivity in patients with varying durations of depressive illness (from 1 week to over 1 year) (28).

The self-report of feeling worst cannot, therefore, be compared to the more clinically relevant measurement of depression offered by the SCL-90-R. Rather, self-reports of feeling worst are most likely to reflect a nonspecific state of dysphoria. The major difference between the bulimia nervosa and comparison groups in terms of seasonal variation was in the areas of binge eating, food intake, and weight, not in depression. Patients with bulimia nervosa therefore appear to be more sensitive to the food intake regulation effects than to the affective impact of seasonal change; previous research suggests that the reverse appears to be true for patients with seasonal affective disorder (2–4).

The close associations of food intake, bulimic symptoms, and seasonal change in bulimia nervosa may be linked to central serotonin activity. That serotonergic mechanisms may be altered in bulimia nervosa has been based on several lines of evidence (29). Kaye et al. (30) have reported low levels of 5-hydroxyindoleacetic acid (5-HIAA) in the CSF of bulimic anorexic patients after weight recovery. Lower CSF 5-HIAA levels have been reported in patients with bulimia nervosa who binge more than two times per day than among less symptomatic patients with bulimia nervosa and comparison subjects (31). Altered peripheral serotonin uptake (32) has been reported, as well as blunted prolactin response to m-chlorophenylpiperazine (33). Bulimia nervosa patients have been reported to reduce binge eating in response to the serotonergic agonists fluoxetine (7) and fenfluramine (8, 34).

That central serotonergic mechanisms may mediate the reported seasonal effects in bulimia nervosa is indirectly supported by Carlsson et al. (35), who have found that hypothalamic serotonin levels (post-mortem analysis of a nonpsychiatric population) are lowest in December through January and rise throughout the rest of the year until peak levels are observed in October through November. Platelet serotonergic uptake also follows a seasonal pattern, with highest levels in the spring and lowest levels in the fall (36). O'Rourke et al. (9, 10) have demonstrated that *d*-fenfluramine is effective in seasonal affective disorder, suggesting that sensitivity to seasonal variations in serotonin levels may be common to both bulimia nervosa and seasonal affective disorder.

The effect of serotonin on binge behavior in bulimia nervosa may be closely associated with the regulation of serotonergic food intake mechanisms. One effect of serotonergic agonists, such as fenfluramine and fluoxetine, for example, is to reduce meal size and rate of food consumption (37). This may be the mechanism by which binge behavior is reduced in bulimia nervosa. Other agents, such as the antidepressants desipramine and imipramine, are also effective in bulimia nervosa (38–40), although probably not because of activation of serotonergic mechanisms. Previously we reported that patients with bulimia nervosa who respond to desipramine have a higher purge frequency and lower urge to binge than do nonresponders (41). The clinical effects of noradrenergic antidepressants may therefore arise from mechanisms that are pharmacologically and behaviorally different from those of serotonergic agonists. Consistent with this notion was the observation that binge eating and purging were dissociated to a degree in study 2. Although there was a correlation, less than 50% of the variance in binge behavior was shared by purge behavior. While binge eating peaked in January, that was the month of lowest purge frequency. Similarly, measures of clinical depression did not vary seasonally, but binge behavior did. Separate biological and psychological processes may therefore be associated with discrete components of bulimic behavior.

In summary, binge eating exhibits marked seasonal patterns in bulimia nervosa, with binge eating being more frequent during seasons characterized by low levels of available light. Dysphoria (but not depression) may also vary seasonally, and there is a higher than normal rate of seasonal affective disorder and subsyndromal seasonal affective disorder in bulimia nervosa. The number of patients presenting to an outpatient eating disorders clinic who met strict *DSM-III* criteria for bulimia was highly related to seasonal changes in photoperiod. The seasonal variation in bulimia nervosa appears to be a primary effect on binge eating, rather than on purge behavior or depression. It is speculated that the seasonal effects are mediated through seasonal variations in central serotonergic mechanisms.

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# Pharmacologic and Cognitive-Behavioral Treatment for Bulimia Nervosa: A Controlled Comparison

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Objective: *This study examined the relative effectiveness of desipramine, cognitive-behavioral therapy, and their combination in the treatment of bulimia nervosa, together with the effects of withdrawing medication after two different lengths of treatment.* Method: *Seventy-one patients meeting* DSM-III-R *criteria for bulimia nervosa, recruited from an eating disorders clinic or by advertisements, were assigned at random to one of five groups: desipramine (withdrawn at 16 or 24 weeks), combined treatment (medication withdrawn at 16 or 24 weeks), and cognitive-behavioral therapy (15 sessions). All treatments were conducted individually in an outpatient clinic. The primary outcome measures were binge eating and purging rates assessed at pretreatment, 16, 24, and 32 weeks. The results were analyzed as three groups (medication, cognitive-behavioral therapy, and combined treatment) at 16 weeks and as five groups at subsequent assessments.* Results: *At 16 weeks, both cognitive-behavioral therapy and the combined treatment were superior to medication given for 16 weeks in reducing binge eating and purging. At 32 weeks, however, only the combined 24-week treatment was superior to medication given for 16 weeks. The combined treatment was also more effective in reducing dietary preoccupation and hunger. Continuing cognitive-behavioral therapy appeared to prevent relapse in patients withdrawn from medication at 16 weeks.* Conclusions: *Overall, the results favor the use of a combination of medication and cognitive-behavioral therapy in the treatment of bulimia nervosa, with medication continued for at least 24 weeks.*

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Two approaches to the treatment of bulimia nervosa, antidepressant medication and variants of cognitive-behavioral therapy, have been shown to be effective in controlled trials (1–3). Imipramine (4, 5), desipramine (6), phenelzine (7, 8), bupropion (9), and fluoxetine (10) have all been found useful. Those receiving active treatment in controlled medication studies reduced their purging by an average of 71%, and 35% of participants stopped purging (3). Dropout rates ranged from 0% to 33% for those receiving active medication. Thus, antidepressant treatment appears promising, although there are some indications that the relapse rate may be significant both while medication is continued and after its withdrawal (11, 12). Neither the extent of relapse after withdrawal from medication nor the differential response to varying durations of antidepressant treatment has been studied in a randomized withdrawal design.

Controlled trials of variants of cognitive-behavioral therapy for bulimia nervosa have been conducted both in individual and group formats (3). Purging was reduced by an average of 77%, with 38% of patients becoming abstinent in the published controlled studies (3). Dropout rates ranged from 0% to 34% for those receiving cognitive-behavioral therapy. These results appear comparable to those of antidepressant treatment, setting the stage for a study comparing the effectiveness of medication and psychological treatments.

To date, only one study has compared the two treatments and their combination (13). In that study, patients with bulimia nervosa were randomly assigned to one of four groups: imipramine, placebo, imipramine combined with group psychotherapy, and placebo combined with group psychotherapy. Group psychotherapy included many of the procedures of cognitive-behavioral therapy, as well as therapist-supervised practice in eating. All three

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active treatments were superior to placebo in reducing binge eating and purging. Group psychotherapy was superior to medication alone. Antidepressant treatment did not add to group psychotherapy in terms of normalizing eating behavior, but it did lead to greater reductions in measures of depression and anxiety.

The present study was designed to investigate three main questions: 1) Which treatment would prove most successful: desipramine, cognitive-behavioral treatment, or their combination? 2) Is there an advantage for prolonged medication treatment? 3) Does continued cognitive-behavioral therapy protect against relapse after discontinuation of medication?

## METHOD

### *Subjects*

Participants were recruited from patients being evaluated in a university eating disorders clinic and by means of advertisements in the local media. After initial telephone screening, eligible subjects were interviewed by staff psychologists or psychiatrists. At this interview the study was described in detail to the potential participant, and informed consent was obtained. A semistructured interview was then completed to ensure that participants met the entry criteria. Criteria for participation included the following: women aged 18–65 years who met *DSM-III-R* criteria for bulimia nervosa, had no concurrent medical condition that would preclude the use of antidepressants, and had no evidence of conduction disturbance on electrocardiography. Exclusion criteria included current anorexia nervosa, drug or alcohol abuse, psychosis, or depression with suicidal risk of sufficient severity to preclude the use of antidepressants on an outpatient basis.

One hundred interviews of potential subjects yielded 71 individuals who participated in the study. Eleven potential participants met an exclusion criterion, and 18 did not wish to continue in the study. Subjects were assigned at random to one of five groups: desipramine continued for 16 or 24 weeks, individual cognitive-behavioral therapy, or the combined treatment with medication continued for either 16 or 24 weeks. Participants were told of their randomization, including the week of medication withdrawal, at the first treatment session.

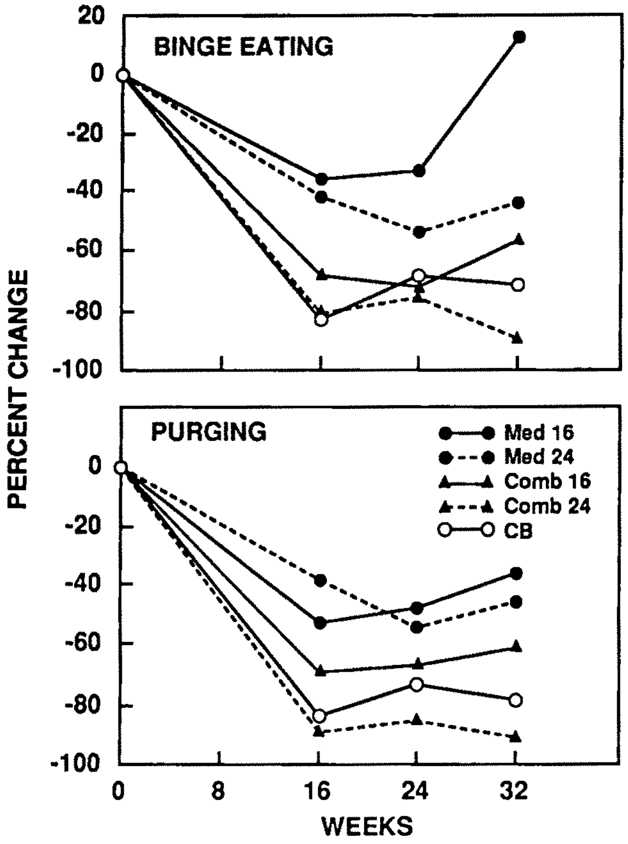
The mean±SD age of the participants was 29.6±8.9 years. Thirty-two percent were married, 56.3% were single, and the remainder were either divorced (8.5%) or separated (2.8%). Fifty-six percent had completed college, 36.7% had completed some college, and the remainder had either completed high school (5.6%) or completed some high school (1.4%); 83% were employed at the time of the study. Binge eating had begun at 19.9±5.7 years of age and purging a few months later at 20.7±5.9 years of age. The participants reported an ideal weight of 53.7±5.8 kg; their weight as measured at baseline was 59.9±9.1 kg. Frequency of purging and binge eating before treatment was 9.2±6.9 times per week and 7.5±5.7 times per week, respectively. Twenty-two percent had been diagnosed as having anorexia nervosa in the past.

### *Procedure*

Medication treatment was guided by a standard protocol detailed in a manual. This treatment was administered by one of the study psychiatrists in sessions averaging 15 minutes. The three study psychiatrists had all had more than 10 years' experience in prescribing antidepressant medication. No psychotherapeutic treatment was given in this condition. The rationale given to patients was that medication had been shown in a significant number of well-controlled studies to stop or decrease binge eating and purging. Participants were given 25 mg of desipramine hydrochloride for the first 3 days, after which the dose was increased to 50 mg. The dose was then increased by 50-mg increments every 3 to 5 days to a maximum of 300 mg, depending on response to treatment and side effects. At 6 weeks, serum levels of antidepressant were obtained and provided to the treating psychiatrist, who used this information to increase or decrease (in the case of toxic levels) the medication dose. At this stage of treatment a maximum of 350 mg of desipramine was allowed. Participants were seen weekly for the first 4 weeks of treatment and then at weeks 6, 8, 12, and 16 for those withdrawn at 16 weeks; those continuing the medication were, in addition, seen at weeks 18, 20, and 24. Medication was withdrawn gradually, usually being completed in 2 weeks, and participants were then seen for two further sessions at 2-week intervals. Thus, those withdrawn at 16 weeks completed their treatment contacts at week 20, while those withdrawn at 24 weeks completed their treatment contacts at week 28.

Cognitive-behavioral treatment was administered individually in 50-minute sessions by Ph.D.-level psychologists with at least 5 years' experience in treating patients with bulimia nervosa. Since a treatment manual is available, the treatment will be briefly described here. (The treatment manual for cognitive-behavioral therapy is available from Dr. Agras; please enclose a check for $10 to cover production and handling costs.) The rationale given for treatment was that social pressure for a thin body leads some women to diet and that the subsequent food deprivation then leads to binge eating, followed by purging in an attempt to control weight. When dietary restraint is reduced, this pattern can be gradually broken. The core treatment procedures included self-monitoring of food intake, binge eating and its circumstances, and purging. In the first part of therapy these data were used to encourage the consumption of three or more well-balanced meals each day. Patients were also encouraged to consume increasing amounts of their feared and avoided foods by adding them to meals. Throughout treatment, cognitive restructuring was used to correct distorted cognitions, for example, rigid food rules and body image concerns. In the last part of therapy, relapse prevention strategies

**FIGURE 1. Change in Binge Eating and Purging Behavior of Patients With Bulimia Nervosa Treated With Medication, Cognitive-Behavioral Therapy (CB), or a Combination**



were used. Participants in this condition received 15 sessions of treatment over the first 16 weeks of the study and were seen in follow-up sessions at weeks 20, 24, and 28.

Weekly meetings were held with the therapists to supervise the medication and psychosocial treatments and to ensure adherence to the study protocol. In addition, randomly selected tape recordings of sessions were audited to ensure that the specific procedures described in the treatment manual were used. Ninety-five percent of the audited tapes included all the procedures described in the manual for that session.

### *Assessments*

Measures were obtained by an assessor who was blind to the participants' treatment assignment. Since binge eating and purging are private behaviors, the primary measures in this study were the frequencies of binge eating and purging, collected by 7-day recall. Other potentially more objective methods, such as serum amylase levels (14) and glycosylated hemoglobin levels (15), have not proven useful. Secondary measures included the Beck Depression Inventory (16), Eating Disorders Inventory (17), Eating Attitudes Test (18), Three Factor Eating Questionnaire (19), Rosenberg Self-Esteem Questionnaire (20), self-efficacy in terms of confidence and ability to practice healthier eating behavior (21), and self-monitored mood states associated with binge eating. Assessments were completed before treatment and at 16, 24, and 32 weeks, although only the frequencies of binge eating and purging were collected at 32 weeks.

### *Data Analysis*

To select and reduce the secondary measures to be used in the final analysis, a principal components analysis of the secondary measures was undertaken. Five factors were found to have eigenvalues greater than 1 and accounted for 68.8% of the variance. The first factor, dietary preoccupation, accounted for 32.8% of the variance. The average of the Eating Attitudes Test dieting subscale and the Eating Disorders Inventory drive for thinness subscale, the subscales most highly correlated with this factor, was chosen to represent this factor. The second factor, mood fluctuation, accounted for 12.3% of the variance and was represented by the mean of the negative mood and urge to binge scores. The third factor, restraint, accounted for 9.6% of the variance and was represented by the cognitive restraint scale of the Three Factor Eating Questionnaire. The fourth factor, self-esteem, accounted for 7.9% of the variance and was represented by the Rosenberg self-esteem scale. The final factor accounted for 6% of the variance and included the disinhibition and hunger subscales of the Three Factor Eating Questionnaire. This factor was termed hunger-disinhibition. Each of these variables was subjected to a repeated measures analysis of covariance (ANCOVA) for the three groups (medication alone, cognitive-behavioral therapy, and the combined treatments) at 16 weeks by using baseline response as the covariate. Similarly, a repeated measures ANCOVA was carried out for five groups at 32 weeks for the primary measures and at 24 weeks for the secondary measures (which were not assessed at 32 weeks). A two-tailed level of significance was used throughout. When a significant Time by Group interaction was found, post hoc tests of the 10 possible pairwise comparisons were carried out. The Bonferroni correction was applied for these comparisons, resulting in an adjusted significance level of $p<0.005$. The primary analyses were conducted by intent to treat, i.e., regardless of whether the participant dropped out of treatment. However, in order to provide additional insights, secondary analyses were also done that included only subjects who completed treatment.

## RESULTS

There were no statistically significant differences between the three or five groups on the sociodemographic measures, the primary outcome measures, or the secondary measures at baseline assessment.

Data were not available for two subjects (2.8%) at the 16-week assessment, for three subjects (4.2%) at 24

**TABLE 1. Characteristics of 71 Patients With Bulimia Nervosa Treated With Medication, Cognitive-Behavioral Therapy, or a Combination**

| | Medication | | | | Medication and Cognitive-Behavioral Therapy[a] | | | | Cognitive-Behavioral Therapy: 24 Weeks (N=23) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 16 Weeks (N=12) | | 24 Weeks (N=12) | | 16 Weeks (N=12) | | 24 Weeks (N=12) | | | |
| Item | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Binges/week | | | | | | | | | | |
| Pretreatment | 5.5 | 4.6 | 5.9 | 5.1 | 7.5 | 3.4 | 9.3 | 5.8 | 8.7 | 7.2 |
| 16 weeks | 3.5 | 6.1 | 3.4 | 3.5 | 2.4 | 3.1 | 1.7 | 1.5 | 1.5 | 2.6 |
| 24 weeks | 3.7 | 7.1 | 2.7 | 2.8 | 2.1 | 2.8 | 2.3 | 4.7 | 2.8 | 5.9 |
| 32 weeks | 6.2 | 13.7 | 3.3 | 3.9 | 3.2 | 4.2 | 1.0 | 3.0 | 2.5 | 3.6 |
| Purges/week | | | | | | | | | | |
| Pretreatment | 9.7 | 9.4 | 6.3 | 4.9 | 8.3 | 4.3 | 11.7 | 5.9 | 10.1 | 7.7 |
| 16 weeks | 4.7 | 8.6 | 3.9 | 3.8 | 2.6 | 3.2 | 1.2 | 2.7 | 1.7 | 2.7 |
| 24 weeks | 5.0 | 10.8 | 2.9 | 3.0 | 2.7 | 4.2 | 1.7 | 4.7 | 2.7 | 5.9 |
| 32 weeks | 6.2 | 13.7 | 3.4 | 4.1 | 3.2 | 4.3 | 1.1 | 3.0 | 2.2 | 3.6 |
| Hunger/disinhibition | | | | | | | | | | |
| Pretreatment | 10.0 | 2.3 | 9.6 | 2.3 | 11.1 | 2.1 | 11.0 | 2.1 | 10.1 | 3.2 |
| 16 weeks | 7.4 | 2.1 | 7.9 | 2.7 | 9.1 | 3.6 | 6.0 | 3.4 | 8.6 | 3.2 |
| 24 weeks | 8.7 | 2.5 | 7.4 | 1.7 | 11.1 | 2.1 | 6.3 | 3.2 | 8.3 | 3.4 |
| Dietary preoccupation | | | | | | | | | | |
| Pretreatment | 14.0 | 4.8 | 13.4 | 5.4 | 15.3 | 3.0 | 15.9 | 3.0 | 14.1 | 4.3 |
| 16 weeks | 9.7 | 4.5 | 10.4 | 6.7 | 10.5 | 7.1 | 5.5 | 2.9 | 9.3 | 5.6 |
| 24 weeks | 8.9 | 4.1 | 7.5 | 5.6 | 10.7 | 7.1 | 5.9 | 6.2 | 9.5 | 6.0 |

[a] Medication withdrawn at 16 and 24 weeks.

weeks, and for five subjects (7.0%) at 32 weeks. Thus compliance with these assessments was excellent.

Of those assigned to receive medication, six participants (12.2%) had stopped medication by 6 weeks, seven (14.6%) by 16 weeks, and eight (17%) by 24 weeks. Reasons for stopping medication included side effects (seven subjects) and moving from the area (one subject). Of those assigned to receive cognitive-behavioral treatment, only one subject (4.3%) stopped treatment. Eighty-eight percent of subjects completed 70% of the cognitive-behavioral treatment sessions.

The mean dose of desipramine at 6 weeks was 168 mg, and at discontinuation of medication it was 167 mg. The mean serum level of desipramine at 6 weeks was 130.8 ng/ml. There were no significant differences between the groups in either medication dose or antidepressant blood levels.

The percent reduction in binge eating and purging for each of the five groups is shown in figure 1, and the mean values for the primary and significant secondary measures are given in table 1. At the 16-week assessment the combined treatment group had reduced purging by 80.9% (64% abstinent), while those receiving cognitive-behavioral treatment alone had reduced it by 82.6% (48% abstinent) and those receiving medication alone had reduced it by 42.7% (33% abstinent). Similar results were found for binge eating. The combined treatment group reduced binge eating by 82.6% (65% abstinent), the cognitive-behavioral group by 81.7% (50% abstinent), and the desipramine group by 38.8% (35% abstinent). There was a significant Time by Group interaction for purging ($F=6.35$, df=2, 65, $p<0.004$) and binge eating ($F=6.0$, df=2, 65, $p<0.005$). For purging post hoc analysis revealed that cognitive-behavioral therapy was superior to medication alone ($p<0.004$), as was the combined condition ($p<0.003$). Similarly, for binge eating both cognitive-behavioral therapy ($p<0.005$) and the combined condition ($p<0.004$) were superior to medication alone.

The analysis of binge eating and purging for the five groups over the 32 weeks of the study revealed a significant Time by Group interaction for both binge eating ($F=2.16$, df=12, 168, $p<0.02$) and purging ($F=2.13$, df=12, 168, $p<0.02$). In the case of purging, the 24-week combined treatment was superior to 16 weeks of medication ($p<0.005$). For binge eating the 24-week combined treatment was superior to medication given for both 16 ($p<0.004$) and 24 ($p<0.005$) weeks. Seventy percent of patients in the 24-week combined condition were then abstinent, compared with 55% for cognitive-behavioral therapy and 42% for 24 weeks of medication.

At 16 weeks there was a significant Time by Group interaction for dietary preoccupation ($F=4.53$, df=2, 62, $p<0.01$), with the combined group superior to the group receiving medication alone ($p<0.005$). At 24 weeks there was a significant Time by Group interaction for the hunger/disinhibition factor ($F=2.45$, df=8, 100, $p<0.02$). Post hoc tests revealed that the 24-week combined treatment was superior to cognitive-behavioral therapy ($p<0.005$).

There was no significant change in weight at either 16 or 24 weeks, with participants averaging a small (0.3 kg) loss in weight at both assessments. There were no significant differences between groups in terms of weight changes.

The intent to treat analyses described earlier in this paper were repeated and included only those participants who completed their respective therapies. The results were identical both for the initial ANCOVA and for the post hoc tests, with the following exception. At

16 weeks, no significant Time by Group interaction was found for the dietary preoccupation factor.

## DISCUSSION

Both the combined treatment and cognitive-behavioral therapy were superior to medication given for 16 weeks in reducing the primary symptoms of bulimia nervosa, namely, binge eating and purging. This finding is similar to that of Mitchell et al. (13), who used a placebo-controlled comparison. These researchers found that group psychotherapy based on cognitive-behavioral principles was superior to imipramine and that there were no differences between cognitive-behavioral treatment and the combined treatment in reducing binge eating and purging. In the present study, however, only the 24-week combined condition was superior to 16 weeks of medication at the 32-week assessment. In addition, the combined condition appeared to reduce associated psychopathology such as dietary preoccupation and hunger. Overall, then, the results of this study suggest that desipramine given for 24 weeks and combined with cognitive-behavioral therapy produces the broadest therapeutic benefits.

Interestingly, as shown in figure 1 and table 1, there was considerable relapse in binge eating for the group treated with medication for 16 weeks. The 24-week combined condition was superior to both the 16- and 24-week medication groups. This suggests that cognitive-behavioral therapy, if continued, may help prevent relapse after withdrawal of medication.

It is important to ascertain whether the effects obtained in this study are similar to those of other controlled studies of medication and cognitive-behavioral treatment. As noted earlier, the median rate of purging cessation after medication treatment in previously reported controlled studies was 35%, a rate exceeded by each of the medication groups in the present study. For cognitive-behavioral treatment, earlier controlled studies suggest an abstinence rate of 38%, while the abstinence rate in our study was 55%. The comparable figures from the Mitchell et al. study (13) were 16% for medication and 51% for group psychotherapy. Thus, the treatment results from the present study were comparable to those obtained in the previous research literature, suggesting that the comparisons between groups fairly represented the usual effects of treatment.

One limitation of this study was that the medication dose and blood levels achieved in this study, while within the therapeutic range, were somewhat low. Higher doses might have been associated with correspondingly better results. However, the abstinence rates achieved in the medication groups in the present study exceeded those of Mitchell et al. (13), who used a higher dose of imipramine and achieved higher blood levels. In addition, since only one medication was used in the present study, the results may not fairly represent what might be attained in clinical practice by using alternative medications for nonresponding patients. Similarly, given the effectiveness of other forms of psychosocial therapy in the treatment of bulimia nervosa, for example, response prevention of purging (22), focal psychotherapy (23), and interpersonal therapy (24), the use of one or more of these forms of treatment for the patient who did not respond to cognitive-behavioral therapy might have improved the results of psychosocial treatment. This question, which has not been investigated in bulimia nervosa, needs to be addressed in future clinical trials.

From a clinical viewpoint, the overall trend in the results of this study supports the use of the combination of medication and cognitive-behavioral treatment as the preferred therapeutic approach to bulimia nervosa, particularly when medication is continued for 24 weeks. These conclusions may, however, be tempered by the planned follow-up of these patients, which is still in progress.

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# Multiple Personality Disorder in Switzerland

Jirí Modestin, M.D.

*Objective: There are no reliable data on the prevalence of multiple personality disorder. The objective of the study was to determine whether and, if so, how frequently patients with multiple personality disorder are encountered and diagnosed in Switzerland. Method: All qualified Swiss psychiatrists were sent a questionnaire on multiple personality disorder along with the* DSM-III *description of multiple personality disorder and three case examples. A total of 836 psychiatrists (66%) answered after two mailings, and 770 questionnaires qualified for evaluation. In addition, a random sample of nonresponders were contacted by telephone. Results: Three percent of the psychiatrists indicated that, at the time of the inquiry, they were treating or examining one or more patients who met* DSM-III *criteria for multiple personality disorder, and 10% indicated that they had seen multiple personality disorder at least once during their professional career. The patients were not equally distributed among the psychiatrists; three colleagues reported that they had seen much higher numbers of patients with multiple personality disorder. The point prevalence of multiple personality disorder among patients seen by psychiatrists in Switzerland amounts to 0.05%–0.1%. Conclusions: Multiple personality disorder appears to be a disorder that genuinely exists, even though it occurs relatively rarely.*

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There is a jarring discontinuity in the number of reported patients with multiple personality disorder (1). A period of high interest in multiple personality disorder toward the end of the last century (2) was followed by a temporary disappearance of the syndrome (3) and a recent sharp increase in reports on multiple personality disorder (4), reaching almost "epidemic" proportions (5). The disorder has been accepted as a diagnostic entity by *DSM-III* and *DSM-III-R*, yet the views regarding its existence and frequency remain controversial; the waves of interest have been attributed to particular, time-linked circumstances (2, 6). Some clinicians, even those well acquainted with the disorder, have encountered few patients with multiple personality disorder during their long professional careers (7, 8), whereas others have come in contact with large series of patients with multiple personality disorder within several years (9, 10). The diagnosis of multiple personality disorder arouses strong feelings: 78% of therapists treating patients with multiple personality disorder encountered intense, half of them even extreme, skepticism in the form of deliberate interference with treatment on the part of their fellow professionals (11). Furthermore, the large majority of reports on multiple personality disorder originate in the United States. The diagnosis of multiple personality disorder may also be relatively frequent in some Dutch psychiatric facilities (12), but it has seldom been given in India (13) and only rarely in Great Britain (14).

There are virtually no reliable data on the prevalence of multiple personality disorder. The study of Bliss and Jeppsen (15) was rightly criticized because of their markedly biased sample (16). The estimate of Adityanjee et al. (13) was based on three patients with multiple personality disorder observed in a single institution. Two further estimates (17, 18) are not substantiated by any appropriate data. Ross (19, p. 90) indicated that multiple personality disorder had "a point prevalence of somewhere between 1 and 50 and 1 and 10,000 persons in urban North America." Again, his broad estimate was based on indirect, soft data. The existing uncertainty is accentuated by some American therapists' astronomically high probability of encountering patients with multiple personality disorder (6).

The present study was undertaken to help solve the perplexing situation. Its purpose was to determine 1) whether and, if so, how frequently patients with multiple personality disorder are encountered and diagnosed in Switzerland, 2) the proportion of Swiss psychiatrists

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who diagnose multiple personality disorder, and 3) the distribution of the frequencies of multiple personality disorder diagnoses by individual psychiatrists.

## METHOD

In February 1989 a letter was sent to all qualified Swiss psychiatrists who were registered in the 1988 yearbook of Swiss physicians or whose names had been considered for the next edition. The letter explained the purpose of the study (to obtain information on whether and, if so, how frequently the diagnosis of multiple personality disorder has been made in Switzerland) and asked for cooperation. It contained the following:

1. A questionnaire asking for data on the professional activity of the psychiatrist, the frequency of his or her diagnosing multiple personality disorder, and some basic characteristics of the patients diagnosed as having multiple personality disorder, including their sex and date of birth. The latter data were requested in order to avoid counting any patient more than once.
2. A copy of the complete *DSM-III* text on multiple personality including the diagnostic criteria.
3. Three classic examples of patients with multiple personality disorder originally reported by Gmelin (in 1791), Azam (1887), and Hodgson (1891/1892) and reproduced in extenso later by Ellenberger (20).

The narrower *DSM-III* definition of multiple personality disorder was given preference in order to exclude questionable cases. Introducing the notion of personality states and accepting various degrees of sharing and commonalities between the personalities in nonclassic cases, the *DSM-III-R* criteria for multiple personality disorder seem to be less stringent and less precise. However, even the *DSM-III* criteria for multiple personality disorder are arbitrary and relatively unelaborated and leave much room for interpretation (16); the omission of amnesia, the "absolutely essential" criterion of multiple personality disorder (21) as a defining characteristic, is especially striking (6).

About 4 months after the letter, a second mailing was sent; it included the same complete set of information and was addressed to all those who had not yet answered. About another 4 months later an effort was made to reach a random sample (every fourth) of the nonresponders by telephone to obtain the pertinent information and to determine how representative the group of responders was of the whole population of Swiss psychiatrists.

## RESULTS

Of the 1,273 psychiatrists who received the questionnaire, a total of 836 (66%) responded after both mailings. Some colleagues did not fill out the questionnaire, the majority of them because they were no longer professionally active. A total of 770 (60%) questionnaires qualified for evaluation. Some questions remained unanswered in individual questionnaires, which explains the different number of responders for individual variables.

The 770 responding psychiatrists (566 [74%] men and 204 [26%] women) came from all parts of Switzerland and worked in all kinds of psychiatric facilities; 460 (62%) of them (N=741) were in private practice. The mean±SD duration of their professional activity (N=709) was 17.5±10.6 years. On average, a psychiatrist working in private practice or in a hospital (N=362) treated or was in charge of 65 patients at the time of this inquiry, whereas the corresponding caseload for a psychiatrist working in public services (N=187) was 98 patients.

The concept of multiple personality disorder had been (at least theoretically) previously known to 436 (61%) of the responding psychiatrists (N=710). The proportion of colleagues who had been acquainted with multiple personality disorder differed according to the setting in which they were working (N=684): private practice, 227 (52%) of 439; private inpatient settings, 16 (73%) of 22; public inpatient settings, 80 (73%) of 110; and public outpatient departments, 92 (81%) of 113 ($\chi^2$=43.20, df=3, p<0.0001). The psychiatrists who had or had not been acquainted with multiple personality disorder previously did not differ in regard to the length of their professional experience.

A total of 19 (3%) of the psychiatrists (N=679) indicated that they treated, were in charge of, or examined at the time of the inquiry patients they would diagnose as having multiple personality disorder according to the *DSM-III* criteria. Two of them had not previously been acquainted with the concept of multiple personality disorder, and four were not sure whether their diagnosis of multiple personality disorder was correct.

Altogether, 63 (10%) of the psychiatrists (N=655) indicated that they had seen at least one patient with multiple personality disorder during their professional career. Eight of them had not previously been acquainted with the concept of multiple personality disorder, and 17 had doubts regarding the diagnosis. The majority (46 of the 63 psychiatists) had seen one patient with multiple personality disorder; six reported having seen two patients, three reported having seen three, and two reported having seen four such patients. Each of the caseloads of five, six, and seven patients with multiple personality disorder was seen by one psychiatrist.

Three other psychiatrists were notable exceptions regarding the distribution of patients with multiple personality disorder. One colleague reported seeing two patients with multiple personality disorder at present and having seen 20 in the past; another colleague reported seeing one at present and 26 in the past, and the third reported seeing 20 at present and at least 59 in the past. These three psychiatrists were contacted. One of them said that she had seen videotapes on multiple personality disorder in the United States and had checked the patients carefully with regard to the symptoms in question; she admitted that *DSM-III* criteria for multiple personality disorder were possibly not met in all cases. I did not succeed in finding any special reason for the high frequency with which the two other colleagues (both men) encountered patients with multiple personality disorder. Both of them maintained that their patients conformed to the *DSM-III* criteria. Nevertheless, the one who diagnosed multiple personality disorder most frequently had not been acquainted with the clinical picture previously; this casts some doubt on his diagnostic reliability.

At the time of the inquiry, 44 patients were diagnosed as having multiple personality disorder by responding Swiss psychiatrists. If one takes into consideration the number of all the patients treated by these psychiatrists, the point prevalence of multiple personality disorder amounts to 0.11%; if the four doubtful cases and the 23 patients seen by the three psychiatrists mentioned earlier are excluded, the point prevalence amounts to 0.04%. If we consider only those patients diagnosed by psychiatrists with previous knowledge of multiple personality disorder, the corresponding point prevalences are 0.08% and 0.06%. Similarly, the responding psychiatrists indicated that during their entire professional careers, they had diagnosed 221 patients (primarily retrospectively) as having multiple personality disorder; this reduces the number of patients with multiple personality disorder to 71 if 22 doubtful cases and those seen by the three psychiatrists mentioned earlier are excluded. These figures indicate that 56 years or 174 years of professional experience, respectively, are needed to encounter one patient with multiple personality disorder. Again, if only patients diagnosed by psychiatrists with a previous knowledge of multiple personality disorder are included, the corresponding figures are 58 years or 121 years, respectively.

There were no differences between the psychiatrists who had ever diagnosed a patient as having multiple personality disorder and those who had not with regard to gender distribution or the part of the country and the kind of setting they worked in. On the other hand, those claiming to have met patients with multiple personality disorder had more frequently been acquainted with the concept of multiple personality disorder previously (50 [86%] of 58 versus 386 [59%] of 652; $\chi^2$=15.27, df=1, p<0.0001), had longer average professional experience (21 years versus 17 years; t=2.87, df=707, p=0.004 [two-tailed]), and had a higher average caseload in 1988 (321 patients versus 172 patients; t=2.72, df=561, p=0.007 [two-tailed]).

As indicated in 65 patients diagnosed as having multiple personality disorder, they were of both genders (33 [51%] were men and 32 [49%] were women), and their mean age at diagnosis was 38±15 years (range=14–74). With regard to the German-, French-, and Italian-speaking parts of the country, their distribution corresponded exactly with the proportion of responding psychiatrists. Thirty-eight (58%) of the patients were seen as outpatients, 23 (35%) as inpatients, and four (6%) in correctional facilities. Forty-eight (74%) were referred primarily for treatment, whereas 17 (26%) were referred for consultation or expert examination.

Of 101 nonresponders contacted by telephone, only 48 were ready to provide the information requested. The remaining psychiatrists no longer practiced, were not interested in the topic, or refused to cooperate without giving a reason. Among nonresponders there was a higher proportion of women (39 [39%] versus 204 [26%]; $\chi^2$=5.93, df=1, p=0.015), and all nonresponders who gave information worked in outpatient settings. There were no differences between responders and nonresponders with regard to the part of the country in which they practiced, whether they worked on a private or public basis, the duration of their professional activity, and their caseload. A smaller proportion of nonresponders had previously been acquainted with the concept of multiple personality disorder (17 [35%] of 48 versus 436 [61%] of 710; $\chi^2$=11.57, df=1, p<0.001). None of the psychiatrists responding on the telephone knew a patient with multiple personality disorder at the time of the inquiry, and only one psychiatrist reported having met a patient with a questionable diagnosis of multiple personality disorder in the past; these figures do not differ in statistical terms from those provided by the responders.

## DISCUSSION

A total of 66% of all Swiss certified psychiatrists returned the questionnaire, and over 90% of the questionnaires were eligible for evaluation. The majority (65%) of nonresponders had not been acquainted with the concept of multiple personality disorder previously, and, as indicated by some of them, this might have been one of the reasons for their nonresponse. Because only one past questionable case of multiple personality disorder could be identified among nonresponders, it seems improbable that unreported cases of diagnosed multiple personality disorder were missed in our survey.

At the time of the inquiry 3% of the responders reported *DSM-III*-defined cases of multiple personality disorder, and 10% had seen such cases during their professional career. Several factors, however, could have influenced these figures. Nonresponders may have seen patients with multiple personality disorder less frequently; the responders were not able to indicate the date of birth in all—mainly past—cases, so that some patients could have been counted more than once; and some patients with multiple personality disorder could have escaped the attention of the psychiatrists with no previous knowledge of the concept of multiple personality disorder. Nevertheless, the influences of these factors will be less pronounced regarding the data related to the time of the inquiry and besides, our proportion of 3% corresponds relatively well with the 4% reported by Ross et al. (22) from Canada. Our findings indicate the point prevalence of multiple personality disorder to be 0.05%–0.10% of patients seen by psychiatrists. Currently, this seems to be the most precise, data-based estimate of such a prevalence of multiple personality disorder; however, it may not be equally valid for other countries. In India, for example, the patients with the same "basic fault" are more likely to develop hysterical psychosis than multiple personality disorder (13), whereas the patients in the United States may more frequently develop multiple personality disorder because of, among other things, the presence of the well-known, media-popularized models and, perhaps, the higher frequency of child abuse.

The average age of our patients with multiple personality disorder at the time of the inquiry does not seem to differ considerably from that reported by others (23). In contrast, there is a clear difference regarding the female-to-male ratio, which was 8–9:1 in American series (5, 22–24) but about 1:1 in the present survey. We can only speculate about the reasons for this difference, pointing to the possible sociocultural influence or to the possibility of the nonhomogeneity of the population with multiple personality disorder (see later discussion). As recently reported (25), many cases of men with multiple personality disorder could have been missed in different studies, and the actual gender ratio may be closer to 1:1.

Three colleagues reported having seen an exceptionally high number of patients with multiple personality disorder. It is highly improbable that these three colleagues would be better diagnosticians or that multiple personality disorder would in some way concentrate in their practice, the more so because two of them indicated no special interest in multiple personality disorder and one of them had not even been acquainted with multiple personality disorder previously. Thus, the same phenomena must have been evaluated differently by these colleagues, or, conversely, the same diagnostic (*DSM-III*) criteria must have been interpreted and applied in a different way. Incidentally, the case of the Hillside strangler demonstrates the difficulties that even the most experienced experts have in diagnosing multiple personality disorder (6). The other possibility is that these colleagues have a different interview and therapy technique suitable to elicit or shape the symptoms in question. Patients with multiple personality disorder are excellent hypnotic subjects (26), and it is possible to suggest the formation of other personalities (27). Concentration on symptoms of multiple personality disorder is mandatory if a diagnosis is to be made because most of the patients with multiple personality disorder hide or deny their symptoms or are not aware of them (28); yet concentrating on symptoms may lead to their reinforcement and entrenchment (14). Experimental enacting of the multiple personality role is a relatively easy task (29).

Does this mean that multiple personality disorder is always an "iatrogenic, largely culture-bound, not naturally occurring symptom complex" (30)? My data do not support this hypothesis. Some well-known, highly distinguished, leading Swiss psychiatrists also reported having seen individual cases of multiple personality disorder. As expected in the case of rare events, the majority of psychiatrists saw no multiple personality disorder or only a very small number of cases. Those who reported patients with multiple personality disorder had been acquainted with the concept of multiple personality disorder more frequently in the past, had a slightly longer average professional experience, and also had a larger caseload. All these factors increase the probability of these psychiatrists seeing patients with multiple personality disorder. Thus, there apparently are patients with multiple personality disorder in Switzerland (even though I have personally never met one). The wide distribution of multiple personality disorder in time and space proves the disorder to be a genuine phenomenon (31).

Many colleagues indicated that they had frequently seen features of multiple personality disorder in their patients but that they had never seen a full picture of completely developed multiple personality disorder. Quite obviously, the tendency to split and to dissociate (more or less pronounced) is ubiquitous, and it finds its expression not only in many works of art (32) but also in many psychiatric concepts and theories (33–36). In some patients this ubiquitous tendency, together with their special individual history and sociocultural influences, will result in the "spontaneous" development of a "genuine" multiple personality disorder. In other patients, however, an iatrogenic influence and secondary gains seem to be probable. It is possible that women are overrepresented in the latter group of patients.

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# Recovery and Major Depression: Factors Associated With Twelve-Month Outcome

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*Objective: In spite of the prevalence and chronicity of major depression, there is no consensus regarding which clinical and psychosocial variables are associated with recovery. The authors examined the probability of recovery from a major depressive episode 12 months after hospital discharge, the factors most closely associated with recovery, and the patterns of improvement distinguishing patients who recovered from those who did not. Method: Seventy-eight inpatients with a* DSM-III *diagnosis of major depression were assessed at hospitalization and at monthly intervals for 12 months after discharge on a variety of clinical and psychosocial factors. Recovery status at 12-month follow-up was then used as a basis for comparing acute-phase patient characteristics and change in symptoms over time. Results: By the 12th month of follow-up, 34 (48.6%) of 70 patients met criteria for recovery. The five most important factors related to recovery were shorter length of hospital stay, older age at onset of depression, better family functioning, fewer than two previous hospitalizations, and absence of comorbid illness. The majority of patients who had recovered by 12 months had done so within 6 months of discharge; the average length of time to recovery was 4.9 months. Conclusions: Patients hospitalized for major depression have less than a 50-50 chance of recovering by 1 year. Some variables associated with nonrecovery (e.g., comorbid illness, poor family functioning) are amenable to clinical intervention; however, findings also suggest that there may be two distinct types of depressive illness with respect to recovery, one that remits quickly and the other with a more prolonged course of illness.*

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Longitudinal studies of patients with major depression have reported similar rates (20%) of chronicity and of continuous well-being (1–3). Results of these studies provide long-term measures for the prognosis of major depression, but they are less useful in predicting short-term outcome or distinguishing a set of factors that may lead to chronicity or remission. Although studies suggest that 33%–53% of depressed patients are likely to recover within a year (4–7), there is no consensus regarding which clinical and psychosocial variables are associated with recovery.

For example, the relationship between severity of depression and recovery is unclear. There is evidence that a long duration of depression before treatment delays the recovery of some patients (8–11), but the effect of number of previous depressive episodes on outcome is equivocal (9, 10, 12–15). The relation of age at onset and age at index episode to recovery status is also inconsistent (14–17).

The relationship between psychosocial factors and prognosis is inconclusive. Family conflict and the absence of family support may predict poor outcomes for depressed patients, and patients with supportive families may have a better prognosis (7, 9, 18). Neither early loss (e.g., loss of a parent before the age of 20) nor recent life events are predictive of chronicity (19). It may be that recent stressful events rather than distant stressful events are related to relapse (20, 21).

Basic reasons for contradictions in reported effects may include variable diagnostic groupings within the samples studied, follow-up periods that range from as little as 3 months after discharge to greater than 10 years, and patients recruited from both inpatient and outpatient settings (17, 20).

In addition, variation in definitions of key concepts such as recovery and relapse, different boundaries used

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for age cutoffs for age at onset, and a range of instruments measuring severity all contribute to differences in any conclusions that can be drawn from the available data. Furthermore, as several studies have shown, interpretation of variable effects often changes when significant bivariate relationships undergo further analysis with multivariate methods.

In this exploratory study we addressed some of these issues by focusing on the following questions: What is the probability of recovery from a major depressive episode by 12 months after hospital discharge? How do clinical and psychosocial factors contribute to the likelihood of recovery? and Is there any pattern that distinguishes patients who recover from those who do not?

## METHOD

### *Subjects*

The subjects were 78 patients with a diagnosis of major depression who were consecutively admitted to an acute-care university-affiliated hospital and who lived with at least one other family member. A trained research assistant administered the affective disorders section of the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (22). Independent chart reviews by two experienced clinicians (G.I.K. and I.W.M.) confirmed that the diagnosis of major depression met *DSM-III* criteria and verified concurrent axis I, II, or III diagnoses.

Agreement on the diagnosis of major depression, the major focus of the study, was 87%, but we have no reliability data on ratings of comorbid illness. The research assistant conducted the DIS blind to chart diagnoses, and clinicians reviewed patient charts blind to the DIS assessment.

Sociodemographic, clinical, and psychosocial information was collected at the acute stage of hospitalization, at 6 and 12 months after hospital discharge, and at monthly intervals following discharge.

Seventy of the 78 patients completed the study. Two were lost to follow-up, two felt they no longer needed care, three refused, and one gave no reason. No apparent differences were found in baseline variables between patients who dropped out and those who remained in the study.

### *Measures*

Information recorded for patients and family members included age, sex, education, marital status, number of years married, household composition, occupation, and income. Socioeconomic status was determined by using the Nock-Rossi Index (23), a measure that uses characteristics of both husband and wife to derive a family's overall status.

Previous hospitalizations, suicidality, family and spouse history of psychiatric illness and alcoholism, and the presence of coexisting disorders were recorded for each patient. Following our standard procedure (24), we determined cortisol levels from blood samples obtained at 4:00 p.m. and 11:00 p.m.

The Modified Hamilton Rating Scale for Depression (25) was used to assess the severity of depression as well as the presence of depressive symptoms.

The DIS confirmed the diagnosis of major depression and provided age at onset of depression, longest previous episode, number of previous depressive episodes, and symptoms of dysthymia.

The Eysenck Personality Questionnaire (26) measured three aspects of personality characteristics: neuroticism, introversion, and psychoticism.

Patients and participating family members completed the Family Assessment Device, a measure of perceived family functioning derived from the McMaster Model of Family Functioning (27, 28).

Clinicians rated the family's functioning with the McMaster Clinical Rating Scale, an objective measure, analogous to the Family Assessment Device, that assesses families on several dimensions of functioning (unpublished paper of I.W. Miller et al.).

Each patient's premorbid family functioning was assessed by the patient's attending clinician on a 3-point scale on which 1=better than average and 3=worse than average.

The Global Adjustment Scale (GAS) (29) measured patients' overall functioning and was assessed on a monthly basis following discharge.

The Social Readjustment Rating Scale (30) was completed at the 6- and 12-month phases by an adult family member.

### *Procedure*

*Acute phase.* During the first week of hospitalization, after providing informed consent to participate in the study, hospitalized patients were given the DIS and the Modified Hamilton Rating Scale for Depression. At this time, patients and family members over 12 years of age completed the Family Assessment Device, and clinicians rated the family's functioning with the McMaster Clinical Rating Scale. The attending psychiatrist rated the family's premorbid functioning at the end of the patient's hospital stay, and the Eysenck Personality Questionnaire was completed during the later part of the patient's hospitalization.

*Follow-up.* On discharge from the hospital, patients were contacted by telephone on a monthly basis. A trained researcher administered the Modified Hamilton Rating Scale for Depression (minus the agitation and retardation items) and assessed the patient's overall functioning using the GAS. This follow-up procedure has been used successfully in previous studies of depressed patients to monitor the course of their illness (31).

In addition to the monthly interviews, patients and their families met with a clinician at 6 and 12 months after discharge. The Social Readjustment Rating Scale and family assessments were collected at these meetings.

This study was naturalistic by design. Although information was collected on treatments received, no attempt was made to influence the amount or type of therapy given to patients. In-hospital treatment and treatment after discharge included individual and family therapy as well as pharmacotherapy.

### *Analyses*

We defined recovery from a depressive episode as a Modified Hamilton Rating Scale for Depression rating of 7 or less for 3 consecutive months. Thus, the earliest possible time a patient could be considered recovered was at the third month after discharge. After recovery, if a patient scored 18 or more on the Modified Hamilton Rating Scale for Depression, he or she was considered relapsed.

Patients were grouped according to their recovery status at the 12th month after hospital discharge. Patients who met the criterion for recovery at 12 months were considered recovered. Patients who had not recovered or had relapsed (N=7), were considered not recovered. We then examined clinical, psychosocial, and family factors that had been collected during hospitalization to see if there were any relationships between acute-phase variables and outcome of depression at 12 months.

Chi-square statistics and t tests were used for bivariate analyses and logistic regression was used for the multivariate analyses in this exploratory study. The latter technique is advantageous when the outcome variable is dichotomous and predictor variables are a mix of discrete and continuous measures (32–35). Where a significant bivariate relationship existed, the factor was included in the multivariate analysis to see 1) whether the association still held and 2) which factors contributed most to a positive outcome. In each regression model used, the response variable was recovery status (0=no, 1=yes).

Although the number of statistical tests in the preliminary analyses may result in some factor being significant by chance, the exploratory nature of this study would argue against making alpha too stringent. However, we attempted to balance the analyses by conducting additional testing with multivariate methods. Also, the alpha value in the regression model was raised to 0.3 to ensure that factors which did contribute to the model were not discarded needlessly (32).

Finally, we examined patterns of depressive symptoms and overall patient functioning by comparing the patients who had and who had not recovered at each monthly interval.

## RESULTS

By the 12th month after discharge, 34 (48.6%) of the 70 patients had recovered from their depression. For those who recovered, the average length of time to recovery was 4.9 months after discharge from the hospital. There were no differences in recovery rates based on patients' age, education, marital status, number of children, socioeconomic status, or number of years married (tables 1 and 2). Gender tended toward significance: men were 2.66 times more likely than women to recover within 1 year. Among the seven patients who relapsed, the average time to recovery and relapse was 5.3 and 8.4 months, respectively.

Clinical and psychosocial factors assessed during hospitalization and significantly related to recovery at 12 months included absence of a comorbid illness, shorter hospital stay, later age at onset of depression, lower neuroticism scores, and better-than-average premorbid family functioning. The number of previous hospitalizations was analyzed as a continuous variable and, following the example of Keller et al. (4), as a dichotomy. When hospitalizations were divided into none or one versus two or more, the relationship with recovery was significant (table 1). The chances of recovery were more than 7 times greater if the patient experienced only one or no other hospitalization.

Factors not related to recovery status included current suicide attempts or suicidal ideation, number of previous depressive episodes, serum cortisol level, current dysthymia, severity of depression (Hamilton scale), and family history of psychiatric illness, suicidality, or alcoholism (tables 1 and 2).

Variables included in the original logistic regression were length of hospital stay, age at onset of depression, neuroticism, number of previous hospitalizations (none or one versus two or more), presence versus absence of a comorbid illness, gender, and premorbid family functioning. Gender and premorbid family functioning did not retain their significance and were dropped from the model.

We added the general functioning scales of the Family Assessment Device and the McMaster Clinical Rating Scale to our regression model to see how well family factors contributed to recovery. We did not use forced entry for any variable in the model, nor did we specify the order of entry. The final model estimates are presented in table 3.

In order of significance, the risk factors associated with 1-year outcome of a depressive episode were 1) length of inpatient hospital stay, 2) age at onset of depression, 3) overall level of perceived family functioning, 4) number of previous hospitalizations, and 5) comorbidity. Variables that did not retain significance in the multivariate analyses were neuroticism, premorbid family functioning, gender, and the clinician's rating of overall family functioning. The final adjusted model explained 21% of the variance and correctly identified 78% of the cases.

Other regression models that we tested included removing the seven patients who had relapsed during the follow-up period, omitting the length of stay variable, excluding the family variable, and substituting dysthymia for comorbidity. None of these models fit the data as well as the model presented in table 3.

We separated patients with major depression plus a concurrent illness from those without a concurrent illness to see if the original model would better fit patients whose major depression was not compounded by a comorbid illness. Premorbid family functioning was

**TABLE 1. Sex, Marital Status, Comorbidity, Suicidality, Hospitalization, and Family History of 70 Depressed Patients Who Did or Did Not Recover by 12 Months After Discharge**

| | Recovered (N=34) | | Not Recovered (N=36) | | Chi-Square Analysis | | |
|---|---|---|---|---|---|---|---|
| Characteristic | N | % | N | % | $\chi^2$ | p | Odds Ratio[a] |
| Gender | | | | | 3.71 | 0.05 | 2.66 |
| Male | 16 | 47.1 | 9 | 25.0 | | | |
| Female | 18 | 52.9 | 27 | 75.0 | | | |
| Marital status | | | | | 0.60 | n.s. | 2.00 |
| Married | 32 | 94.1 | 32 | 88.9 | | | |
| Not married | 2 | 5.9 | 4 | 11.1 | | | |
| Comorbidity | | | | | 6.89 | 0.01 | 3.66 |
| Major depression only | 22 | 64.7 | 12 | 33.3 | | | |
| Depression plus other psychiatric or medical illness | 12 | 35.3 | 24 | 66.7 | | | |
| Current suicidal ideation | | | | | 0.00 | n.s. | 1.00 |
| No | 11 | 33.3 | 12 | 33.3 | | | |
| Yes | 22 | 66.7 | 24 | 66.7 | | | |
| Current suicide attempt | | | | | 0.22 | n.s. | 1.41 |
| No | 28 | 84.9 | 29 | 80.6 | | | |
| Yes | 5 | 15.2 | 7 | 19.4 | | | |
| Previous hospitalizations | | | | | 7.04 | 0.01 | 7.11 |
| None or one | 32 | 94.1 | 25 | 69.4 | | | |
| Two or more | 2 | 5.9 | 11 | 30.6 | | | |
| Family psychiatric history | | | | | 0.19 | n.s. | 1.24 |
| No | 14 | 41.2 | 13 | 36.1 | | | |
| Yes | 20 | 58.8 | 23 | 63.9 | | | |
| Family history of alcoholism | | | | | 0.17 | n.s. | 1.25 |
| No | 26 | 76.5 | 26 | 72.2 | | | |
| Yes | 8 | 23.5 | 10 | 27.8 | | | |
| Family history of suicide | | | | | 1.25 | n.s. | 2.58 |
| No | 32 | 94.1 | 31 | 86.1 | | | |
| Yes | 2 | 5.9 | 5 | 13.9 | | | |
| Current dysthymia | | | | | 3.44 | 0.06 | 2.53 |
| No | 22 | 66.7 | 15 | 44.1 | | | |
| Yes | 11 | 33.3 | 19 | 55.9 | | | |

[a] First category versus second category. For example, male patients were 2.66 times as likely as female patients to recover within 1 year, married patients were twice as likely to recover as unmarried patients. Odds of 1.00 for suicidal ideation mean even odds of recovery whether or not a patient had suicidal ideation.

**TABLE 2. Socioeconomic Characteristics, Length of Illness, Cortisol Levels, and Psychometric Test Scores During Acute Phase of 70 Depressed Patients Who Did or Did Not Recover by 12 Months After Discharge**

| | Recovered (N=34) | | Not Recovered (N=36) | | Two-Tailed t Test | | |
|---|---|---|---|---|---|---|---|
| Characteristic | Mean | SD | Mean | SD | t | df | p |
| Age (years) | 43.4 | 15.24 | 40.6 | 10.95 | –0.88 | 68.0 | n.s. |
| Education (years) | 12.6 | 2.30 | 13.1 | 2.68 | 0.88 | 67.0 | n.s. |
| Married (years) | 20.3 | 13.75 | 17.1 | 11.95 | –1.02 | 66.0 | n.s. |
| Socioeconomic status[a] | 59.4 | 8.86 | 62.1 | 8.48 | 1.19 | 55.0 | n.s. |
| Number of children | 1.2 | 1.15 | 1.4 | 1.38 | 0.60 | 68.0 | n.s. |
| Length of stay (days) | 18.6 | 7.2 | 26.8 | 11.90 | 3.50 | 58.2 | 0.001 |
| Age at onset (years) | 34.9 | 14.9 | 28.0 | 11.90 | –2.07 | 63.0 | 0.05 |
| Number of previous depressive episodes | 4.7 | 8.2 | 11.5 | 23.50 | 1.58 | 41.7 | n.s. |
| Cortisol level (ng/dl) | 3.6 | 3.9 | 4.2 | 4.10 | 0.45 | 46.0 | n.s. |
| Hamilton depression scale score | 40.5 | 7.9 | 42.1 | 7.30 | 0.84 | 68.0 | n.s. |
| Neuroticism score on the Eysenck Personality Questionnaire | 16.2 | 4.5 | 18.3 | 4.10 | 2.02 | 67.0 | 0.05 |
| Premorbid family functioning score | 2.13 | 0.79 | 2.5 | 0.67 | 2.04 | 62.0 | 0.05 |

[a] Measured by the Nock-Rossi Index (23).

predictive of prognosis for patients with major depression and no concurrent illness, but length of hospital stay predicted recovery for the patients with major depression plus a concurrent illness.

To see if any pattern of improvement distinguished the recovered patients from those who were not, we tracked the severity of depression from the acute phase and global functioning from month 1 (figure 1). There

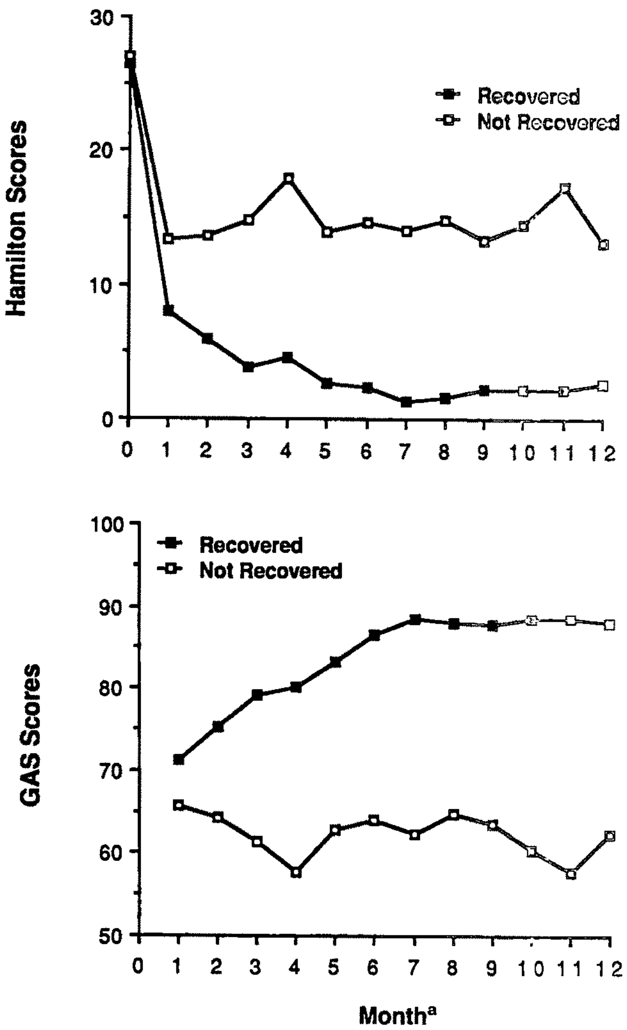
TABLE 3. Logistic Regression Analyses of Risk Factors for Recovery at 12 months of 65 Depressed Patients[a]

| Risk Factor | Beta | SE | Exponential Beta[b] | $\chi^2$ | p |
|---|---|---|---|---|---|
| Length of stay (days) | –0.115 | 0.056 | 0.891 | 6.05 | 0.01 |
| Age at onset (years) | 0.057 | 0.025 | 1.059 | 5.05 | 0.03 |
| Family Assessment Device—general functioning (range=1–4) | –1.779 | 0.829 | 0.169 | 4.61 | 0.03 |
| Number of previous hospitalizations (0=none or one, 1=two or more) | –1.799 | 1.026 | 0.165 | 3.07 | 0.08 |
| Comorbidity (0=no, 1=yes) | –0.978 | 0.642 | 0.376 | 2.32 | 0.13 |

[a] Values were missing for five of the patients; these patients were dropped from this analysis. Model $\chi^2$=28.7, df=5, $L^2$=61.27 (p=0.0001), R=0.456, $R^2$=0.208.

[b] A negative coefficient and multiplier less than 1 indicate a negative relationship with recovery. For example, one more day in the hospital lessened the odds of recovery, an older age at onset increased the chances of recovery.

FIGURE 1. Pattern of Improvement in 70 Depressed Patients Who Did or Did Not Recover by 12 Months After Discharge



[a] For the Hamilton scale, p<0.01 at 1 month and p<0.001 at 2 months (two-tailed t test). For the GAS, p<0.01 at 2 months. For both scales, p<0.001 at months 3–12 (two-tailed t test).

were no differences at the initial assessment between the patients who did and did not recover. The gap in scores between the two groups became significant after only 1 month; thereafter, the recovered patients showed steady improvement throughout the study period.

At the 12-month evaluation an adult family member completed the life events checklist of the Social Readjustment Rating Scale by noting any event that occurred in the previous 6 months. On average, the recovered patients reported significantly fewer events than did those who did not recover (2.9 versus 6.7, t=3.79, df=38.3, p<0.001). Although individual item analysis suggested that positive and negative events occurred to both patients who did and those who did not recover, the percentage of negative events checked was larger for the patients who did not recover than it was for those who recovered (57% versus 33%, $\chi^2$=4.01, df=1, p<0.05).

Patients were asked at the 12-month follow-up about treatment received since their discharge from the hospital. There were no differences between patients who did and did not recover in the percentage who received individual or family therapy. During the follow-up period 22 (71%) of the patients who recovered and 30 (86%) of those who did not received individual therapy ($\chi^2$=2.14, df=1, n.s.); 11 (36%) of the patients who recovered and 15 (43%) of those who did not received family therapy ($\chi^2$=0.37, df=1, n.s.). Not surprisingly, patients who had not recovered by 12 months were more likely to be still receiving pharmacotherapy than those who had recovered (61% [N=22] versus 41% [N=14], $\chi^2$=2.78, df=1, p<0.10).

## DISCUSSION

This exploratory study was designed to focus on factors affecting the course of depressive illness and 12-month outcome. Based on our data, the odds of recovering from a depressive episode within 1 year are 0.94:1, slightly less than a 50-50 chance and similar to other 1-year recovery rates reported in the literature (4–7).

We found that recovery is associated with being male and having a shorter hospital stay, fewer than two previous hospitalizations for depression, older age at onset of depression, lower neuroticism scores, fewer life events reported, no other psychiatric or medical condition, better-than-average premorbid family functioning, less family dysfunction, and better global adjustment after discharge.

Recovery was not associated with marital status, socioeconomic status, severity of the illness at hospitalization, number of previous depressive episodes, suicidality, serum cortisol level, treatment received, or family history of psychiatric illness, alcoholism, or suicidality. Although recovery was associated with comorbidity, we did not find a relationship between a particular type of comorbid illness and recovery status (36).

Multivariate analyses indicated five factors that were the most important in predicting recovery: length of hospital stay, older age at onset of depression, better family functioning, fewer than two previous hospitalizations, and absence of any concurrent illness.

How do these five factors fit into what is known about variables affecting recovery in depression? A shorter hospital stay for patients who were recovered by 1 year would suggest that these patients had a less severe depression; however, there were no differences between patients who did and did not recover in severity of depression at the time of hospitalization as measured by the Modified Hamilton Rating Scale for Depression. Also, length of hospital stay was not significantly correlated with severity of depression.

The family environment of the patient may be salient in that a shorter hospital stay for the recovered patient may be due to a more supportive and better functioning family system. Although family functioning at the acute phase was not related to the length of hospital stay, it was associated with recovery.

We have reported that depressions compounded by other axis I, II, or III disorders significantly prolong the length of hospitalization (36). Although comorbid illness may not increase the severity of depression, a concurrent illness does introduce complicating factors that may lengthen hospital stay and thus affect recovery.

Correlations between length of hospital stay and the other variables in the model were neither substantial nor significant. Further, when length of stay was excluded from the model, the amount of variance explained was reduced to 14% and only 66% were correctly classified. A shorter hospital stay may simply mean that, for some patients, the recovery process starts early in their hospitalization. Alternately, length of hospitalization may reflect other factors not assessed in this study, such as hospital and treating physician philosophies, patient preference, and, increasingly, health coverage.

The association between recovery and older age at onset of depression supports a similar finding by Greenhouse et al. (10); however, our follow-up period was not long enough to determine whether this variable was associated with either recurrence or relapse (15, 17). Patients who were younger at onset of depression (younger than age 30) were more likely to have a psychiatric illness in the family and tended to have poorer family functioning than patients who were older at onset. It may be that patients with an early onset have a higher vulnerability for psychiatric illness and, because of years of stress on the family system, impaired competence in family functioning, both resulting in a more difficult course.

Family functioning factors, seldom included in research on the course of depressive illness, proved to be important in the recovery process. Our finding that poor family functioning at the acute phase was related to poor prognosis is shared by other researchers and has some empirical support (7, 37, 38). A more detailed report on the different dimensions of family function and dysfunction and changes over the course of the depressive episode is forthcoming.

Number of previous depressive episodes did not help to predict course of illness, but the number of previous hospitalizations was predictive of prognosis. However, only when previous hospitalizations were dichotomized to none or one versus two or more did the relationship become significant. Although our figure was lower than that of Keller et al. (12), we were able to replicate the finding of a threshold effect regarding previous hospitalizations. It is unclear whether this finding was a statistical anomaly, but it has some research support and potentially important clinical implications.

Female depressed patients with no concurrent illness were significantly less likely to recover than their male counterparts. Sargeant et al. (39) found an age-gender interaction associated with persistence of depression: older female patients had the most chronic course. The relationship of gender to the course and outcome of major depression is still unclear and is another area that needs further systematic study.

The effect of life events on recovery is also unclear. Some have argued that life events lose their impact in a relatively short period (21, 40). In our study, however, patients who did not recover reported significantly more life events than patients who recovered. It may be that the events included chronic strains or that the patients who did not recover continued to experience new burdens. Although we note the relationship, at this point we are unable to speculate on causal direction.

Finally, a majority of the patients who were recovered at 12 months had, in fact, remitted in less than 6 months after discharge. This suggests that early improvement in the depressive episode may be conducive to long-term improvement or, possibly, to a longer interval of well-being between depressive episodes. It is also possible that there are at least two types of depressive illness with respect to recovery: one that remits quickly and another with a more prolonged course irrespective of treatment given. In the former case, most treatment will be effective, but the latter case represents a challenge to identify which treatment, or combination of treatments, can play a greater role in bringing about a more rapid recovery.

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# Anxiety Syndromes as Epiphenomena of Primary Major Depression: Outcome and Familial Psychopathology

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*Objective: Anxiety symptoms often appear within depressive episodes, but their significance is uncertain. This study sought to determine whether they indicate the coexistence of a separate disease process and whether they have prognostic significance. Method: A series of patients with primary depression who entered a follow-up and family study included 37 who also had obsessions or compulsions, 93 who had panic attacks, 101 who had phobias, and 196 who had none of these anxiety syndromes. Each of the overlapping groups defined by the presence of a specific anxiety syndrome was compared to the group that had none of these syndromes with respect to baseline demographic, phenomenological, and historical features, illness rates among directly interviewed relatives, and diagnostic stability and clinical outcome at semiannual follow-ups over a period of 5 years. Results: Depressive symptoms at intake were more longstanding and severe among patients with specific anxiety symptoms, and these patients went on to experience more depressive morbidity during the ensuing 5 years. The development of autonomous anxiety disorders was rare, however, and specific anxiety syndromes in the probands did not increase risks for the corresponding disorders among relatives. Conclusions: When restricted to episodes of major depression, anxiety syndromes appear to be prognostically significant epiphenomena rather than indicators of an additional disorder.*

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Anxiety syndromes, specifically those characterized by phobias, panic attacks, obsessions, or compulsions, co-occur with major depression at rates far exceeding those explicable by chance (1). This co-occurrence may reflect causal relationships. Depression may be complicated by obsessions, compulsions, phobias, or panic attacks, or the reverse may be true; i.e., anxiety disorders may give rise to depression. Alternatively, anxiety and depressive syndromes may be expressions of a common diathesis. None of these hypotheses is exclusive of the others; causal relationships may exist in some cases, and other cases may reflect, instead, a common etiology. Indeed, there is empirical evidence for each of these possibilities.

The common diathesis hypothesis can be tested in several ways. First, family study data would offer support if a proband diagnosis of anxiety disorder increased risks for depressive disorder among relatives and, conversely, if a proband diagnosis of depressive disorder raised familial risks for anxiety disorders. In particular, probands with coexisting anxiety and affective syndromes should have relatives with increased risks of both of the corresponding disorders. Most of the relevant family studies have not satisfied these predictions, however. Three studies (2–4) compared probands with panic disorder to normal control probands, and none of them found group differences in risks for affective disorders among relatives. Two studies (5, 6) compared probands with affective disorders to normal control probands; one (6) found an increase in panic disorder among the relatives of affective disorder probands, but the other (5) did not. While most twin studies have not provided the diagnostic detail necessary to investigate this question, Torgersen (7) described 13 monozygotic twin pairs in which one twin had panic disorder. Although four co-twins also had panic disorder, none of them had an affective disorder.

Finally, two studies have described the familial psychopathology of probands with coexisting major depression and panic disorder. One of these (8) found increased rates of anxiety disorders only among the families of probands who had had panic attacks when major depression was absent. Probands who had experienced panic attacks only in the context of depressive episodes had no higher familial rates of anxiety disorder than those of depressed probands who did not have panic attacks. In contrast, Leckman et al. (9) found in-

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creased risks for both depression and panic disorder among the relatives of probands with both syndromes regardless of the temporal relationships between these syndromes. The former study (8) may merit more weight, since it determined familial loading entirely from directly interviewed relatives and assessed probands as they presented for the treatment of active symptoms. Leckman et al. (6) only indirectly evaluated a majority of the relatives described. Moreover, they assessed probands during a community survey, and many probands described only past depressive episodes. We suspect that such methods inadequately separate relatives or probands with panic disorder from those with affective disorders.

Studies of diagnostic stability also apply, and these have consistently failed to support the common diathesis concept. Depressed patients who lacked a history of independent anxiety disorders very rarely developed such disorders during follow-up (10, 11). However, neither of these two studies identified subgroups with prominent anxiety symptoms when follow-up began. Diagnostic stability in these particular patients would more directly address the common diathesis hypothesis.

Thus, family study and diagnostic stability data tentatively favor the view that these syndromes coexist because they are causally related. Virtually all well-studied psychiatric illnesses increase risks for major depression (12), and there is no reason to suspect that the anxiety disorders are exceptions to this rule. The reverse may occur as well, and, in fact, a small literature shows that various anxiety syndromes do complicate affective disorders. Coryell et al. (8) and VanValkenburg et al. (13) characterized patients who experienced panic attacks only within depressive episodes, Schapira et al. (14) described phobias precipitated by depression, and several other reports (15–20) concerned obsessions and compulsions temporally confined to depressive episodes. Only the studies of depression with panic attacks (8, 13) described the prognostic significance of these phenomena. Both found that panic attacks were associated with relatively poor outcomes. Whether other anxiety syndromes have similar prognostic significance remains an open question.

To address the issues we have described, the following analyses focus on depressed patients who, at the beginning of follow-up, reported anxiety syndromes temporally confined to depressive episodes. We first consider support for the common diathesis hypothesis. Do these patients often develop autonomous anxiety disorders during follow-up that correspond to the anxiety symptoms present at intake? Are the relatives of these patients at increased risk for the corresponding anxiety disorders or for anxiety disorders in general? Next, we consider the practical implications of anxiety syndromes limited to depressive episodes. Do these coexisting syndromes adversely affect prognosis? If so, are the different anxiety syndromes prognostically equivalent? Finally, are certain outcomes such as suicidal behavior, manic episodes, and substance abuse more or less likely among these patients?

## METHOD

Earlier reports have detailed the family study (21) and 5-year follow-up (12) components of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. Patients with major depression, mania, or schizoaffective disorder were invited to participate shortly after hospital admission or within 2 months of their first outpatient visit. All subjects were 17 years of age or older, Caucasian, English-speaking, knowledgeable about both biological parents, and free of any brain syndrome, terminal illness, or mental deficiency (IQ <70). Individuals entered the study at one of five sites: Massachusetts General Hospital and Harvard University in Boston, Rush-Presbyterian-St. Luke's Medical Center in Chicago, University of Iowa College of Medicine in Iowa City, New York State Psychiatric Institute and Columbia University in New York, and Washington University School of Medicine in St. Louis.

Trained research assistants reviewed medical records for each proband, administered the Schedule for Affective Disorders and Schizophrenia (SADS) (22), and used the resulting information to generate Research Diagnostic Criteria (RDC) diagnoses (23). They then used the Longitudinal Interval Follow-Up Evaluation (24) to conduct semiannual follow-up assessments.

The Longitudinal Interval Follow-Up Evaluation provided weekly ratings of psychopathology for each of the RDC affective and nonaffective disorders. "Recovery" required 8 contiguous weeks with no more than one or two symptoms at no more than a mild degree. "Relapse" presupposed "recovery" and required the definite reappearance of the corresponding syndrome. This instrument also quantified psychosocial adjustment in diverse areas and tracked relevant events such as hospitalization, outpatient contact, and suicide attempts.

Raters systematically described all treatment directed at psychopathology. These data were first condensed into drug equivalences determined by reference to the relevant literature (available from the first author on request) and then into composite antidepressant scores (25). "Active somatic antidepressant" therapy in the following analyses implies more than 100 mg/day of imipramine or its tricyclic antidepressant equivalent, more than 30 mg/day of phenelzine or its monamine oxidase inhibitor (MAOI) equivalent, any lithium therapy, or any ECT.

Many of these patients were also invited to participate in a family study in which all first-degree relatives 17 years of age or older who could be located and who were willing were interviewed by raters blind to proband diagnosis. The SADS—Lifetime Version (SADS-L) provided structure to these interviews and, as with the probands, medical records were sought and reviewed. Attempts were then made to reinterview each of these relatives 6 years later. Research assistants repeated the SADS-L to review lifetime diagnoses and carefully documented any psychopathology that had appeared since the first interview.

The present report concerns only patients who entered the study with definite primary depression; thus, those with histories of any of the nonaffective RDC disorders listed in the criteria for secondary depression (23) were excluded. Patients with "primary depression and phobia" had clinically significant phobias (scores of 3–6 on SADS item 267) during their index episodes of depression. Those with "primary depression and panic attacks" had met criteria for definite panic attacks (a score of 3 on SADS item 251) during their index episodes, and those with "primary depression and obsessions or compulsions" had these symptoms at the definite level (scores of 3–6 on SADS item 270). These three groups were not mutually exclusive; for instance, some patients with primary depression and panic attacks also had phobias. The final, comparison group, however, was exclusive; patients with "uncomplicated primary depression" had no panic attacks, phobias, obsessions, or compulsions as just defined.

We derived several subscales to quantify the severity of depressive symptoms at intake. In contrast to such traditional severity measures as the Hamilton Rating Scale for Depression (26), the "criteria depression score" used here reflected only the criteria symptoms for RDC major depression. The score was calculated by adding the ratings for each of the corresponding SADS items. For some criteria symptoms, several SADS items applied, and the highest item rating was used. Since there were eight criteria symptoms plus dysphoria, the maximum score was 54. The "endogenous depression score" encompassed those symptoms which constituted RDC endogenous depression. Two of the corresponding SADS items, middle and terminal insomnia, had binary scoring and were arbitrarily assigned values of 3. The total maximum possible endogenous depression score was therefore 51.

Since the patient groups with coexisting primary depression and anxiety were not exclusive of each other, they were not compared statistically. Instead, each of the cosyndromal groups was compared pairwise with the group of patients who had primary depression and no anxiety syndrome. Analyses used t tests for continuous variables and Fisher's exact tests for categorical variables. All p values reported here reflect two-tailed tests.

We used Kaplan/Maier life-table methods (27) for comparisons of times to recovery and times to relapse. These techniques describe all subjects to the point at which they recovered or left the study, so that the effects of censored data were minimized. Group sizes for life-table analyses reflected all subjects with at least 6 months of follow-up and therefore differed from those that considered only subjects who completed all 5 years of follow-up.

## RESULTS

Of 359 patients who entered the study with primary major depression and who completed 5 years of follow-up, 163 (45.4%) exhibited at least one of the specified anxiety syndromes. While the majority (N=95, 58.3%) reported only one of these syndromes, many reported two: 11 (6.7%) had both obsessions or compulsions and panic attacks, 16 (9.8%) had both obsessions or compulsions and phobias, 46 (28.2%) had both panic attacks and phobias, and five (3.1%) had all three types of anxiety symptoms.

### *Demographics and Clinical Features*

At intake, depressed patients with anxiety syndromes described longer episode durations than did patients with no anxiety syndrome (table 1). A regression analysis undertaken to control for the effects of group overlap revealed that panic attacks were independently associated with longer durations (F=9.98, df=1, 355, p=0.002), whereas phobic symptoms (F=0.68, df=1, 355, p=0.41) and obsessive-compulsive symptoms (F=1.89, df=1, 355, p=0.17) were not.

Depressed patients with anxiety syndromes were also generally younger at intake and when first depressed than were patients without anxiety. Patients with anxiety syndromes did not differ from patients without anxiety on Global Assessment Scale (GAS) (28) scores at intake or on levels of optimum functioning in the previous 5 years (table 1). However, the two scales designed to reflect depressive symptoms specifically revealed significantly greater severity among patients with anxiety syndromes.

Again, regression analyses revealed that panic attacks, but not obsessions and compulsions or phobias, were associated with higher symptom levels after control for coexistence of the other two anxiety syndromes; for the endogenous depression score, F=6.70, df=1, 355, p=0.01; for the criteria depression score, F=5.04, df=1, 355, p=0.03. Similarly, controlled associations between obsessions and compulsions or phobias and either the endogenous depression score or the criteria depression score failed to approach significance (no p value was <0.10).

Depressed patients with panic attacks were significantly less likely than nonanxious depressed patients to have bipolar I depression (table 2). Otherwise, they were as likely as patients without anxiety syndromes to have each of the specific depressive subtypes considered. Patients with obsessions or compulsions recalled significantly poorer adolescent friendship patterns than did depressed patients without anxiety syndromes (table 1).

### *Familial Psychopathology*

The families of probands with depression and anxiety syndromes had the same rates of primary depression as did the families of probands with uncomplicated primary depression (table 3). Both phobic and obsessive-compulsive disorders were more common among family members of probands with panic attacks, although panic disorder was not. None of the other anxiety disorders was overrepresented in the families of depressed probands with specific anxiety symptoms.

Since proband groups differed significantly by age,

TABLE 1. Age, Clinical, and Historical Data at Intake on Patients With Primary Major Depression Without and With Anxiety Syndromes

| | No Anxiety Syndrome (N=196) | | Obsessions or Compulsions (N=37) | | | | Panic Attacks (N=93) | | | | Phobias (N=101) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | t (df=231) | p | Mean | SD | t (df=287) | p | Mean | SD | t (df=295) | p |
| Age at intake (years) | 41.1 | 15.5 | 37.5 | 17.0 | | n.s. | 37.2 | 13.8 | –2.0 | 0.04 | 36.0 | 13.2 | –3.0 | 0.003 |
| Age at first episode of major depression (years) | 31.1 | 14.7 | 25.4 | 14.2 | –2.2 | 0.03 | 27.6 | 11.4 | –2.3 | 0.03 | 27.1 | 11.7 | –2.5 | 0.01 |
| Duration of index episode (weeks) | 51.5 | 75.8 | 118.4 | 146.1 | 2.7 | 0.01 | 97.3 | 154.7 | 2.7 | 0.008 | 91.6 | 132.3 | 2.8 | 0.006 |
| GAS score at intake | 41.8 | 13.1 | 40.9 | 12.5 | | n.s. | 43.3 | 11.8 | | n.s. | 42.7 | 12.5 | | n.s. |
| Criteria depression score | 37.2 | 6.7 | 39.2 | 4.7 | 2.1 | 0.04 | 39.5 | 4.7 | 3.4 | 0.001 | 39.1 | 5.1 | 2.7 | 0.007 |
| Endogenous depression score | 29.8 | 6.9 | 31.1 | 5.8 | | n.s. | 32.1 | 5.4 | 3.1 | 0.002 | 31.4 | 6.2 | 2.0 | 0.05 |
| Best level of social relations in past 5 years[a] | 2.9 | 1.0 | 2.9 | 0.9 | | n.s. | 2.7 | 1.1 | | n.s. | 2.8 | 1.0 | | n.s. |
| Best level of overall functioning in past 5 years[b] | 2.3 | 1.0 | 2.5 | 1.0 | | n.s. | 2.3 | 1.0 | | n.s. | 2.4 | 1.0 | | n.s. |
| Adolescent friendship patterns[c] | 2.8 | 0.9 | 3.3 | 0.9 | 3.1 | 0.002 | 2.9 | 1.0 | | n.s. | 3.0 | 1.1 | | n.s. |

[a] Possible scores range from 1 to 7; 7=grossly inadequate.
[b] Possible scores range from 1 to 6; 6=major impairment.
[c] Possible scores range from 1 to 6; 6=grossly inadequate.

TABLE 2. Sex, Marital Status, and Diagnostic Subtypes at Intake of Patients With Primary Major Depression Without and With Anxiety Syndromes

| | No Anxiety Syndrome (N=196) | | Obsessions or Compulsions (N=37) | | Panic Attacks (N=93) | | Phobias (N=101) | |
|---|---|---|---|---|---|---|---|---|
| Variable | N | % | N | % | N | % | N | % |
| Female sex | 123 | 62.8 | 23 | 62.2 | 63 | 67.7 | 74 | 73.3 |
| Ever married | 139 | 70.9 | 20 | 54.1[a] | 64 | 68.8 | 61 | 60.4 |
| Bipolar I subtype | 36 | 18.4 | 5 | 13.5 | 6 | 6.5[b] | 14 | 13.9 |
| Bipolar II subtype | 22 | 11.2 | 1 | 2.7 | 18 | 19.4 | 11 | 10.9 |
| Psychotic subtype | 32 | 16.3 | 9 | 24.3 | 12 | 12.9 | 24 | 23.8 |
| Definite endogenous subtype | 121 | 61.7 | 23 | 62.2 | 69 | 74.2 | 70 | 69.3 |

[a] Significantly different from group with no anxiety syndrome ($\chi^2$=4.1, df=1, p=0.04).
[b] Significantly different from group with no anxiety syndrome ($\chi^2$=7.2, df=1, p=0.007).

we used logistic regression to control for proband age. The results were virtually unchanged and, again, only the relatives of probands with panic attacks differed significantly from the relatives of probands with uncomplicated primary depression. The former were significantly more likely to have obsessive-compulsive disorder ($\chi^2$=4.4, df=1, p=0.04) or phobic disorder ($\chi^2$= 11.9, df=1, p=0.0006). This pattern remained when we compared groups by the proportions with positive family histories.

The most prominent type of phobia (agoraphobia, social phobia, simple phobia, or mixed phobias) was scored for 30 of the 32 individuals who had phobic disorder and who were relatives of depressed probands with panic attacks. Agoraphobia was most prominent in nine individuals (30.0%), social phobia in none, simple phobia in 16 (53.3%), and mixed phobias in five (16.7%). This distribution did not differ significantly from that for the 37 individuals who had phobic disorder and were relatives of probands without anxiety syndromes; the corresponding numbers and proportions were eight (21.6%), three (8.1%), 19 (51.4%), and seven (18.9%), respectively. Thus, the association between panic attacks among probands and phobic disorder among their relatives was not specific to agoraphobia.

### *Diagnostic Stability*

Of the 37 patients who entered this study with primary depression and obsessions or compulsions, 28 recovered. Of these, 14 (50.0%) developed at least one

**TABLE 3. Illness Rates Among Twice-Interviewed Relatives of Patients With Primary Major Depression Without and With Anxiety Syndromes**

| | No Anxiety Syndrome | | | Obsessions or Compulsions | | | Panic Attacks | | | Phobias | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | N | N | % | N | N | % | N | N | % | N | N | % |
| Interviewed relatives | 444 | | | 69 | | | 180 | | | 203 | | |
| With primary major depression | | 129 | 29.1 | | 21 | 30.4 | | 54 | 30.0 | | 68 | 33.5 |
| With obsessive-compulsive disorder | | 1 | 0.2 | | 1 | 1.5 | | 4 | 2.2[a] | | 3 | 1.5 |
| With panic disorder | | 10 | 2.3 | | 4 | 5.8 | | 3 | 1.7 | | 5 | 2.5 |
| With phobic disorder | | 37 | 8.3 | | 7 | 10.1 | | 32 | 17.8[b] | | 22 | 10.8 |
| With generalized anxiety disorder | | 39 | 8.8 | | 8 | 11.6 | | 19 | 10.6 | | 20 | 9.9 |
| Families | 126 | | | 22 | | | 60 | | | 61 | | |
| With primary major depression | | 77 | 61.1 | | 14 | 63.6 | | 36 | 60.0 | | 43 | 70.5 |
| With obsessive-compulsive disorder | | 1 | 0.8 | | 1 | 4.6 | | 4 | 6.7[c] | | 3 | 4.9 |
| With panic disorder | | 10 | 7.9 | | 3 | 13.6 | | 3 | 5.0 | | 3 | 4.9 |
| With phobic disorder | | 29 | 23.0 | | 6 | 27.3 | | 24 | 40.0[d] | | 17 | 27.8 |
| With generalized anxiety disorder | | 31 | 24.6 | | 8 | 37.4 | | 19 | 31.7 | | 20 | 32.8 |

[a] Significantly different from group with no anxiety syndrome (p=0.03, Fisher's exact test).
[b] Significantly different from group with no anxiety syndrome (p=0.001, Fisher's exact test).
[c] Significantly different from group with no anxiety syndrome (p=0.04, Fisher's exact test).
[d] Significantly different from group with no anxiety syndrome (p=0.007, Fisher's exact test).

**TABLE 4. Categorical Measures of Outcome During 5-Year Follow-Up for Patients With Primary Major Depression Without and With Anxiety Syndromes**

| | No Anxiety Syndrome (N=196) | | Obsessions or Compulsions (N=37) | | Panic Attacks (N=93) | | Phobias (N=101) | |
|---|---|---|---|---|---|---|---|---|
| Measure | N | % | N | % | N | % | N | % |
| Recovered from index episode | 182 | 92.9 | 28 | 75.7[a] | 83 | 89.3 | 95 | 94.1 |
| In episode of major depression at follow-up | 44 | 22.5 | 10 | 27.0 | 23 | 24.7 | 30 | 29.7 |
| In hospital at follow-up | 95 | 48.5 | 25 | 67.6[b] | 43 | 46.2 | 53 | 52.5 |
| Psychologically serious suicide attempt | 23 | 9.6 | 4 | 9.5 | 13 | 11.8 | 12 | 10.2 |
| Committed suicide | 7 | 2.9 | 0 | 0.0 | 1 | 0.9 | 1 | 0.9 |
| Mania or schizoaffective mania during follow-up | 37 | 18.9 | 6 | 16.2 | 8 | 8.6[c] | 15 | 14.9 |
| Hypomania during follow-up | 35 | 17.9 | 5 | 13.5 | 19 | 20.4 | 25 | 24.8 |
| Alcoholism during follow-up | 15 | 7.7 | 1 | 2.7 | 4 | 4.3 | 8 | 7.9 |
| Drug use disorder during follow-up | 5 | 2.6 | 1 | 2.7 | 8 | 8.6[d] | 6 | 5.9 |
| Impaired psychosocial adjustment at 5 years | 99 | 50.5 | 27 | 73.0[e] | 59 | 64.1[c] | 64 | 64.7[c] |
| Received somatic antidepressant therapy | 146 | 74.5 | 28 | 75.7 | 75 | 74.3 | 68 | 73.1 |

[a] Significantly different from group with no anxiety syndrome (p=0.004, Fisher's exact test).
[b] Significantly different from group with no anxiety syndrome (p=0.05, Fisher's exact test).
[c] Significantly different from group with no anxiety syndrome (p=0.04, Fisher's exact test).
[d] Significantly different from group with no anxiety syndrome (p=0.03, Fisher's exact test).
[e] Significantly different from group with no anxiety syndrome (p=0.02, Fisher's exact test).

new episode of major depression, but only two (7.1%) developed separate episodes of obsessive-compulsive disorder. Of the 196 patients with primary depression and no anxiety syndrome, 182 recovered and, of these, 78 (42.9%) developed new episodes of major depression and three (1.6%) developed separate episodes of obsessive-compulsive disorder. The risks for new episodes of obsessive-compulsive disorder in these two groups were not significantly different.

Patients who began the study with panic attacks (N=93) were similarly unlikely to develop autonomous panic disorder. Of the 83 patients who recovered, 44 (53.0%) developed new episodes of major depression, but only five (6.0%) developed autonomous episodes of panic disorder. However, this risk was significantly higher than that seen for patients who entered the study with no anxiety syndrome; none of these patients developed separate episodes of panic disorder (p=0.003, Fisher's exact test).

New episodes of phobic disorder were somewhat more common than were new episodes of panic disorder or obsessive-compulsive disorder. Of the 95 patients who began follow-up with primary major depression and phobias and went on to recover, 46 (48.4%) had new episodes of major depression and 12 (12.6%) had new, discrete episodes of phobic disorder. Five (2.6%) of the 196 patients who began follow-up with no anxiety syndrome developed phobic disorder ($\chi^2$= 10.7, df=1, p=0.005).

### *Course and Outcome*

Depressive symptoms were more persistent and recurrent among patients with coexisting anxiety syn-

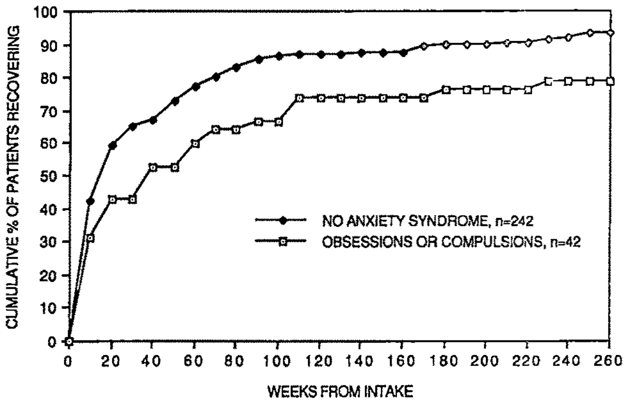
**TABLE 5. Continuous Measures of Outcome During 5-Year Follow-Up for Patients With Primary Major Depression Without and With Anxiety Syndromes**

| | No Anxiety Syndrome (N=196) | | Obsessions or Compulsions (N=37) | | | | Panic Attacks (N=93) | | | | Phobias (N=101) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | t (df=231) | p | Mean | SD | t (df=287) | p | Mean | SD | t (df=295) | p |
| Number of weeks depressed | 27.2 | 36.5 | 59.5 | 68.3 | 2.8 | 0.008 | 40.3 | 47.9 | 2.3 | 0.02 | 38.0 | 40.1 | 2.3 | 0.02 |
| Number of weeks of antidepressant therapy | 47.0 | 69.7 | 47.6 | 64.3 | | n.s. | 54.5 | 68.6 | | n.s. | 59.3 | 73.9 | | n.s. |
| GAS score | | | | | | | | | | | | | | |
| At 6 months | 62.1 | 17.4 | 55.4 | 15.4 | –2.2 | 0.03 | 58.6 | 14.1 | | n.s. | 58.4 | 13.0 | –2.1 | 0.04 |
| At 2 years | 67.2 | 14.9 | 55.3 | 16.1 | –4.4 | 0.0001 | 65.7 | 14.9 | | n.s. | 63.3 | 15.2 | –2.1 | 0.03 |
| At 5 years | 65.7 | 15.1 | 58.4 | 17.1 | –2.6 | 0.009 | 62.8 | 15.5 | | n.s. | 60.8 | 16.3 | –2.6 | 0.01 |

dromes than they were among patients without anxiety syndromes, although many pairwise comparisons did not reach significance (tables 4 and 5). The anxious patients had considerably longer median times to recovery; patients with no anxiety syndromes took a median of 14 weeks to recover, while those with obsessions or compulsions took 39.5 weeks ($\chi^2$=5.3, df=1, p=0.02), those with panic attacks took 20 weeks, and those with phobias took 28 weeks ($\chi^2$=5.0, df=1, p=0.03). Moreover, among those who recovered, anxiety syndromes were associated with shorter times to relapse. The median time to relapse was 80 weeks for those without anxiety syndromes but 37 weeks for those with obsessions or compulsions, 62 weeks for those with panic attacks, and 44 weeks for those with phobias (significantly different from those without anxiety syndromes, p=0.03, Fisher's exact test).

Of the three anxiety syndromes, obsessions and compulsions clearly had the gravest prognostic significance. Figure 1 incorporates all subjects who completed at least 6 months of follow-up and shows that this outcome difference emerged in the first year of follow-up. Time to recovery among these patients was twice that for patients without anxiety syndromes, and this group ranked lowest on all of the six measures of persistence or recurrence of depressive symptoms. Similarly, both the GAS scores and the raters' global assessments of psychosocial functioning ranked patients with obsessions or compulsions as last, or most impaired, at 6 months, 2 years, and 5 years of follow-up.

**FIGURE 1. Recovery From Index Episode of Primary Major Depression of Patients With No Anxiety Syndrome and Patients Who Also Had Obsessions or Compulsions**[a]



[a]Significant difference between groups ($\chi^2$=5.3, df=1, p=0.02).

Regression analyses were conducted for the outcome measures that most robustly distinguished patients with anxiety syndromes from those without anxiety syndromes: likelihood of recovery from the index episode, number of weeks depressed during follow-up, GAS score at 2 years, and GAS score at 5 years. After control for coexistence of panic attacks and phobias, the presence of obsessive or compulsive symptoms strongly predicted a lower rate of recovery ($\chi^2$=11.8, df=1, p=0.0006) and a greater number of weeks depressed during follow-up ($\chi^2$=13.8, df=1, p=0.0002). The presence of phobias predicted a low rate of recovery at a nearly significant level ($\chi^2$=3.2, df=1, p=0.07) after control for the coexistence of the other two anxiety syndromes. The presence of obsessions or compulsions also predicted lower GAS scores at 2 years (F=16.6, df=1, 355, p=0.0001) and, at a borderline significance level, at 5 years (F=3.6, df=1, 355, p=0.06). The relation between phobic symptoms at intake and GAS score at 5 years also approached significance (F=3.2, df=1, 355, p=0.07). None of the other anxiety syndrome/outcome relationships approached significance after control for other coexisting anxiety syndromes. To recapitulate, the presence of obsessions or compulsions predicted, at highly significant levels, a lower rate of recovery, more weeks depressed during follow-up, and a lower GAS score at 2 years, even after statistical control for other anxiety syndromes. The relations between phobic symptoms and outcome approached significance for the likelihood of recovery and for the GAS score at 5 years.

We next considered the possibility that patients with anxiety symptoms had poorer outcomes because they were at least somewhat more likely to manifest separate anxiety disorders. To explore this, we repeated the comparisons displayed in table 4 after excluding the patients who developed autonomous anxiety disorders during follow-up. The results were essentially unchanged. One difference (patients with obsessions or compulsions were significantly more likely to be hospitalized during follow-up) became nonsignificant when diagnostically unstable patients were excluded. However, two other insignificant differences became significant; patients with panic attacks now had a significantly shorter median time to relapse (56.0 weeks; $\chi^2=3.9$, df=1, p=0.05) and significantly lower (worse) GAS scores at 6 months (mean±SD=58.0±13.8; t=–2.2, df=208.9, p=0.03).

Approximately three of every four patients received active antidepressant therapy at some time during follow-up, and the aggregate duration of such therapy was slightly more than 1 year (tables 4 and 5). None of the anxiety syndromes was associated with a higher likelihood of antidepressant therapy. Patients with these complications were no more or less likely than patients without them to receive such therapy, nor were any anxiety syndromes associated with treatment sustained for greater or lesser periods.

## DISCUSSION

The direct and repeated interviews of relatives undertaken in this study revealed little evidence that anxiety syndromes confined to episodes of primary depression implied separate disease processes. Probands with depression and coexisting anxiety syndromes had relatives with no less risk for primary depression than relatives of probands with uncomplicated primary depression, and the complicating anxiety syndromes were not reflected in increased risks for the corresponding disorders among relatives. Probands with panic attacks had increased familial loadings for obsessive-compulsive disorder and phobic disorder, but this pattern has not been noted previously and was thus unexpected. Specifically, Noyes et al. (4) found no increase in phobic disorder among the relatives of panic disorder probands. Therefore, our finding must be replicated before it is given weight in generating or supporting hypotheses. On balance, the lack of specificity between proband anxiety syndromes and familial anxiety disorders argues against the common diathesis hypothesis described previously.

These analyses leave unclear the prognostic primacy of any of these syndromes over the others. Obsessions and compulsions were clearly the most important predictors of morbidity when the course of illness was tracked prospectively. However, a retrospective view at intake revealed panic attacks as the more important correlate of severity and chronicity. Also, phobias independently predicted several outcome measures at levels approaching statistical significance. These data, while they indicate a prognostically complex interrelationship among these syndromes, permit the tentative conclusion that panic attacks and obsessions or compulsions are the more important of the three.

Depressed patients with associated obsessions or compulsions, panic attacks, or phobias were unlikely to develop these symptoms as autonomous disorders during follow-up. They were much more likely to develop, instead, further episodes of primary depression. These findings accord with earlier studies that showed high diagnostic stability for primary depression (10, 11), although the test of stability applied in the present study was more rigorous, since these subjects were particularly prone to diagnostic instability. The small but significant level of diagnostic change that did occur may indicate imperfections in the temporal sequencing of syndromes; that is, some patients may have failed to recall previous, autonomously occurring anxiety disorders. On the other hand, some individuals may suffer from two illnesses; data from this study, though, suggest that such coincidences are very infrequent.

Although the anxiety syndromes identified predicted very little diagnostic instability, they nevertheless had prognostic importance. The depressed patients with any one of these anxiety syndromes had poorer outcomes than did the depressed patients without an anxiety syndrome. If these symptoms simply implied the presence of the corresponding anxiety disorder, a poorer outcome in these patients would be entirely unsurprising. However, follow-up showed that very few patients actually had autonomous anxiety disorders, and the prognostic disadvantage conveyed by these anxiety symptoms was undiminished after the exclusion of diagnostically unstable patients from the analysis. These symptoms, then, appear to be epiphenomena which, like delusions (29), signify a more severe and persistent illness.

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# A Double-Blind Comparison of Valproate and Lithium in the Treatment of Acute Mania

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*Objective: This study was carried out to compare the efficacy of lithium carbonate with that of valproate in acute mania and to determine whether pretreatment clinical characteristics, such as the presence of a mixed affective state, might predict a differential response to the two drugs. Method: Twenty-seven patients meeting* DSM-III-R *criteria for acute manic episodes underwent a 3-week, randomized, double-blind, parallel-groups trial of treatment with lithium carbonate or valproate. Symptom severity was measured by using the Schedule for Affective Disorders and Schizophrenia, change version (SADS-C), the Global Assessment Scale (GAS), and the Brief Psychiatric Rating Scale (BPRS). Drug effects were compared by using repeated measures analysis of variance (ANOVA). Results: At the end of the study, nine of 14 patients treated with valproate and 12 of 13 patients treated with lithium had responded favorably, as measured by changes in the SADS-C mania, BPRS, and GAS scores. Elevated pretreatment SADS-C depression scores were associated with good response to valproate. ANOVA revealed a significant interaction between drug and mixed affective state with respect to treatment response. Conclusions: Lithium and valproate were both effective in improving manic symptoms, and lithium was slightly more efficacious overall. Unlike the case with lithium, favorable response to valproate was associated with high pretreatment depression scores. Therefore, treatment with valproate alone may be particularly effective in manic patients with mixed affective states.*

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Lithium salts are the standard treatment for acute episodes of mania. Despite the efficacy and relative lack of ill effects of lithium, a substantial number of patients with manic disorder do not respond to treatment with lithium alone. The best-defined groups of patients who do not respond well to lithium are those with mixed affective states (1–3) and with four or more cycles per year (4). Of these groups, patients with mixed presentations are the more common, representing 30%–50% of manic episodes (1). However, prospective treatment trials provide essentially no information about effective regimens for the mixed state.

Emrich et al. (5, 6) and Post et al. (7) suggested that certain drugs previously used as anticonvulsants, including carbamazepine and valproate, may be effective in manic episodes. These drugs would be especially useful if they were effective in patients who would not be expected to respond well to lithium. Data from retrospective studies suggest that valproate may be effective in patients with rapid cycling (8) and that open treatment with valproate was effective in mixed states (9). As a preliminary investigation of differential predictors of response to lithium compared with valproate, we have carried out a double-blind, parallel-groups trial of lithium versus valproate in patients admitted to our clinical research unit with acute manic episodes.

## METHOD

Twenty-seven patients, 21 women and six men, were admitted to our clinical research unit. The patients were consecutive admissions meeting *DSM-III-R* criteria for a manic episode. After giving informed consent, patients entered a 4–7-day placebo washout period during which the *DSM-III-R* diagnosis of manic episode was

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confirmed independently by two board-certified psychiatrists (J.L.C., M.D.L., or A.C.S.) using a semistructured interview and a *DSM-III-R* checklist. Baseline clinical ratings and medical and laboratory evaluations, including physical and neurological examinations, CBC, liver and thyroid function tests, electrolytes, EEG, and ECG (if the patient was over 50 years old), were completed during this period. Patients with abnormal EEG, liver function, thyroid function, or hematologic findings were excluded from the study, as were patients with positive urine drug screens and patients with focal neurological abnormalities. Patients were also excluded if they had *DSM-III-R* diagnoses of drug or alcohol dependence or drug or alcohol abuse within 12 months before admission or before the onset of major affective episodes. Eight subjects assigned to valproate and seven subjects assigned to lithium had histories of drug or alcohol abuse at some point during the course of their bipolar disorder.

Other clinical characteristics of the two groups were also comparable. Time since the first episode averaged 12.3±6.2 years (range=0–22) for valproate patients and 8.8±5.9 years (range=0–20) for lithium patients; each group included one patient having a first manic episode. Twelve patients in the valproate group had been treated with lithium; seven had failed to respond at least once. In the lithium group, 10 patients had previously been treated with lithium, and six had at least one treatment failure. No patients had ever received valproate.

Patients were assigned randomly to treatment with lithium or valproate in a double-blind fashion. The lithium group, consisting of 10 women and three men, received lithium citrate as the elixir, starting at 0.5 meq/kg per day. The dose of lithium was increased until either a maximum dose of 1800 mg/day, level of 1.5 mmol/liter, dose-limiting side effects, or clinical improvement occurred. Lithium levels at the end of the study ranged from 0.8 to 1.4 mmol/liter. The valproate group, consisting of 11 women and three men, was started on a fixed-dose regimen of valproate as the elixir. Valproate patients received 1500 mg/day during the first week, 2250 mg/day during the second week, and 3000 mg/day during the third week, unless their symptoms had remitted or they experienced dose-limiting side effects. Valproate levels were 85±17 μg/ml (range=67–118) at the end of the first week, 98±27 μg/ml (range=71–147) at the end of the second week, and 98±17 μg/ml (range=65–126) at the end of the third week. Medicine was given three times a day, diluted by the research pharmacist to a total volume of 30 ml with flavored diluent.

Plasma drug levels were monitored on days 5–7 of each week, the results were sent to the research pharmacist, and the dose was adjusted by a nonblinded, nontreating physician. The Schedule for Affective Disorders and Schizophrenia, change version (SADS-C) (10), the Global Assessment Scale (GAS) (11), and the Brief Psychiatric Rating Scale (BPRS) (12) were administered at the time of dose adjustments.

Rescue medication, including chloral hydrate and lorazepam, was allowed for extreme behavioral problems not responding to nonpharmacological interventions. The amount of rescue medication needed did not differ between the treatment groups: the patients assigned to valproate received 2.9±5.9 g of chloral hydrate and 5.7±5.9 mg of lorazepam and the patients assigned to lithium received 4.4±5.4 g of chloral hydrate and 5.0±5.6 mg of lorazepam. Four patients in each group required no rescue medication.

Five patients out of the 27 whose outcomes were evaluated did not complete the full 21-day protocol but dropped out after 8–20 days of treatment. These included two patients assigned to valproate (one responder and one nonresponder) and three patients assigned to lithium (two responders and one nonresponder). Patients dropped out because of deterioration, recovery, or desire to leave the study. No patients had to leave the study because of adverse drug effects.

Statistical comparisons used Student's two-tailed t test or analysis of variance (ANOVA), as described in the Results section. Categorical response and nonresponse were defined essentially as described by Secunda et al. (1). An improvement in the SADS-C mania factor of at least 50% was defined as a favorable outcome. Patients whose pretreatment SADS-C depression scores were greater than 30 were defined as having mixed mania. There were four patients with mixed mania in each drug treatment group.

## RESULTS

Comparison of the lithium and valproate treatment groups revealed no significant differences in initial BPRS, GAS, or SADS-C factor scores (Student's t test). There were also no differences between the groups in age or sex.

Nine of the valproate patients and 12 of the lithium patients had favorable outcomes after 3 weeks of treatment. In neither group did responders differ from nonresponders with respect to drug doses or plasma drug levels or in pretreatment SADS-C mania scores.

Table 1 shows initial and final SADS-C mania scores for all patients treated with lithium and with valproate and for responders to the two drugs. Pretreatment mania scores were nonsignificantly higher in patients assigned to valproate. Neither pretreatment scores nor scores after treatment differed significantly between lithium- and valproate-treated patients. Repeated measures ANOVA, however, showed a significant drug group effect, and posttreatment mania scores were higher in patients given valproate.

Table 1 also summarizes the effects of lithium and valproate on BPRS scores and on global impairment as measured by the GAS. As with the SADS-C mania factor, the effects of treatment appeared highly significant. In addition, there was a trend toward a significant group effect for BPRS scores. Table 1 also shows the SADS-C depression scores in responders and nonresponders to valproate before and after treatment. Pre-

**TABLE 1. SADS-C Mania, BPRS, GAS, and SADS-C Depression Scores of Patients With Acute Mania Before and After Treatment With Valproate or Lithium**

| | Score | | | |
|---|---|---|---|---|
| | Before Treatment | | After Treatment | |
| Test and Group | Mean | SD | Mean | SD |
| SADS-C mania[a] | | | | |
| All patients given valproate (N=14) | 52.9 | 12.3 | 27.1[b] | 20.9 |
| Patients who responded to valproate (N=9) | 54.2 | 9.8 | 12.9 | 9.2 |
| All patients given lithium (N=13) | 43.4 | 20.3 | 10.2[b] | 8.8 |
| Patients who responded to lithium (N=12) | 44.7 | 20.6 | 9.0 | 8.2 |
| BPRS total[c] | | | | |
| All patients given valproate (N=14) | 28.4 | 9.4 | 10.6 | 9.1 |
| All patients given lithium (N=13) | 24.1 | 9.8 | 4.3 | 5.7 |
| GAS[d] | | | | |
| All patients given valproate (N=14) | 30.9 | 14.9 | 61.9 | 20.8 |
| All patients given lithium (N=13) | 27.6 | 12.6 | 71.2 | 14.6 |
| SADS-C depression | | | | |
| All patients given valproate (N=14) | 18.9 | 15.9 | 9.1 | 8.4 |
| Patients who responded to valproate (N=9) | 25.6[e] | 15.8 | 9.0 | 8.9 |
| Patients who did not respond to valproate (N=5) | 7.0[e] | 6.3 | 9.4 | 7.5 |
| All patients given lithium (N=13) | 23.6 | 9.5 | 5.7 | 8.1 |

[a] Repeated measures ANOVA: group effect, F=7.13, df=1, 25, p=0.013; response effect, F=45.8, df=1, 15, $p<10^{-4}$; interaction, F=0.75, df=1, 25, n.s.

[b] Significant difference in posttreatment score between all patients given valproate and all patients given lithium (t=2.12, df=25, $p<0.05$).

[c] Repeated measures ANOVA: group effect, F=3.2, df=1, 25, p=0.08; response effect, F=76.9, df=1, 25, $p<10^{-4}$; interaction, F=0.4, df=1, 25, n.s.

[d] Repeated measures ANOVA: group effect, F=0.73, df=1, 25, n.s.; response effect, F=85, df=1, 25, $p<10^{-5}$; interaction, F=2.9, df=1, 25, n.s.

[e] Significant difference between responders and nonresponders to valproate (t=2.3, df=12, $p<0.05$).

treatment depression scores were significantly higher in valproate responders than in nonresponders.

Examination of response in patients with mixed versus nonmixed mania revealed that all four patients with mixed mania receiving valproate responded, but five of 10 patients with nonmixed mania responded. Unlike the case with valproate, a mixed state was associated with relatively unfavorable response to lithium: the one lithium nonresponder had a mixed presentation, and posttreatment mania scores were significantly higher in the four patients with mixed mania (18.0±4.5) than in the nine patients with nonmixed mania (6.7±8.0) treated with lithium (t=2.3, df=11, $p<0.05$). ANOVA revealed a significant interaction between mixed presentation and drug treatment outcome (F=4.2, df=1, 25, $p<0.05$), lending further support to the possibility that lithium and valproate differ in their effects on patients with mixed and nonmixed mania.

## DISCUSSION

Only a small number of patients have been studied in controlled treatment trials with valproate (8). The 64% response to valproate found in the current study was similar to the findings of previous reports. Pope et al. (13) recently reported a 53% response rate to valproate in a placebo-controlled study, but their patients were selected for previous nonresponse to or intolerance of lithium. The response to lithium in our patients was somewhat higher than generally reported. Overall, lithium appeared to be slightly more efficacious than valproate. The difference was clearest among patients with nonmixed mania: all nine of the patients with nonmixed mania given lithium responded to it, but five of 10 patients with nonmixed mania given valproate responded to that drug. In contrast to the case with lithium (1), a mixed state appeared to be associated with better response to valproate: responders had higher pretreatment depression scores than did nonresponders (table 1), and the rate of response was higher in patients with mixed mania than in patients with nonmixed mania. These data, although preliminary, suggest that valproate and lithium may be effective in different groups of manic patients.

Table 1 shows that depressed mood, as well as mania, improved in patients treated with valproate. We previously reported that lithium improved depression in patients with mixed mania (14). Unlike valproate, however, lithium did not improve manic symptoms in these patients.

Valproate has a number of characteristics that make it an attractive alternative treatment for patients with bipolar disorder. The drug is generally well tolerated, does not induce hepatic metabolism of itself or of other drugs, and has relatively few interactions with psychotropic drugs (15). These features may make valproate a useful adjunct in the treatment of complicated patients who do not respond to single agents and a possible alternative treatment for patients who generally respond less well to lithium, such as patients with mixed mania. There are some disadvantages to its use, however. Valproate is teratogenic and should be used with caution in fertile women (16). Valproate can cause mild to moderate elevations in hepatic enzymes and has been linked to severe liver damage, especially in children (17). Other side effects that may be troublesome include weight gain and alopecia.

Although the results of this study suggest that patients with mixed mania may respond relatively well to valproate, they should be interpreted with caution. The sample was not large, women were overrepresented, the response rate to lithium was unusually high, and the patients assigned to valproate appeared to be more severely ill. It will be valuable to undertake larger studies investigating pretreatment clinical factors associated with nonresponse to lithium and response to alternative treatments.

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# *DSM-IV* and New Diagnostic Categories: Holding the Line on Proliferation

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*The authors discuss aspects of the decision-making process for including "new" diagnostic categories in* DSM-IV. *They detail the different kinds of new categories proposed for inclusion in* DSM-IV *and discuss the risks and benefits of incorporating them. The authors comment on whether new diagnostic categories should be included in official nosologies as a stimulus for research or as a culmination of research. They also highlight problems with "sunsetting" diagnoses. The criteria for change in* DSM-IV*—a way to deal with the expanding array of proposals for additional diagnostic entities—are discussed. The authors also offer a series of specific examples of the different kinds of new categories being considered for inclusion in* DSM-IV.

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There has been a tendency for official nomenclatures to recognize more and more diagnostic categories. In 1840 the U.S. census included only one category for mental disorders. The 1880 census was expanded to include seven different categories of mental disorders. In 1917 the Committee on Statistics of the American Psychiatric Association developed a classification system incorporating 59 disorders (1). By the time of *DSM-I,* in 1952, the diagnostic system had grown to 106 categories. In 1968 *DSM-II* included a total of 182 diagnostic categories. The biggest spurt came with *DSM-III,* in which the number of categories reached 265, and in *DSM-III-R* the increase continued to 292 categories.

The pressure to add new categories or to split existing ones has continued unabated. In the last 2 years of our work on *DSM-IV,* we have received 94 suggestions for new diagnostic categories. Some of these suggestions represent considerable thought and effort by distinguished researchers and clinicians in the field. Others have been offered more as tentative ideas requiring further elaboration. The suggestions also vary in the degree to which they draw on historical tradition and/or have a significant empirical foundation.

The major rationale for most new diagnoses suggested for *DSM-IV* is the perceived need to increase the coverage of the system. The proposed new diagnosis is intended to describe a pattern of symptoms not captured in the existing categories. In some cases the new category represents a construct that is not already included in *DSM-III-R* (e.g., acute stress disorder, dementia with mixed Alzheimer's and vascular features). In other instances the proposed category represents a specific subtype of an existing disorder with purported treatment implications or other clinical implications (e.g., atypical depression, postpartum depression). In still other cases the suggested new category is similar to currently existing categories but subthreshold in its requirements (e.g., "minor depression" to fill the niche for describing depression of a severity that is associated with impairment but which does not meet the criteria for major depression or the duration criteria for dysthymia and which is not associated with a particular stressor as in adjustment disorder).

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There are two ways to make new diagnostic distinctions in *DSM-IV:* inclusion of either new diagnostic categories or new subtypes or modifiers. Proposals for new categories have included establishing specified codes and rubrics or labels as well as full sets of criteria. Two examples, acute stress disorder and mixed anxiety and depression, are discussed in detail later. Proposals for adding a subtype to, or providing a "modifier" or a specification for, an already existing disorder generally, although not always, do not include establishing a separate code. There have been suggestions for subtyping bulimia nervosa, specifying that atypical or reverse vegetative features are present in several types of mood disorders, and indicating the presence of self-injurious behavior that accompanies certain disorders.

In this article we discuss the implications of incorporating additional diagnoses in *DSM-IV.* We begin with an evaluation of the benefits and risks in determining the appropriate coverage of *DSM-IV.* Next, we discuss whether new diagnoses should be added to *DSM-IV* as a way of stimulating research or whether they should be included in the official nomenclature only as the culmination of already existing and convincing research. We also discuss why it is more difficult to eliminate old categories than to incorporate new ones. Given these considerations, we explain the criteria we are applying in the development of *DSM-IV* to help us make decisions about proposed diagnostic categories. Finally, to illustrate issues raised in this article, we examine three diagnostic categories that have been proposed for inclusion in *DSM-IV.*

## RISKS AND BENEFITS OF INCORPORATING ADDITIONAL DIAGNOSTIC CATEGORIES

Those who identify the need for a new diagnostic category are often concerned that the lack of a specific category with criteria, rubric, and codes will result in a condition being ignored by practitioners, researchers, and educational programs. Placement in the "not otherwise specified" diagnostic categories, which are provided for residual conditions and other conditions not explicitly discussed elsewhere and which now include many categories being proposed for *DSM-IV,* is often considered inadequate. At the same time, there is almost always a considerable price to pay for the increased coverage provided by any new category. The benefit of more precise diagnoses for some individuals must be balanced against the risk of making incorrect diagnoses for other individuals (i.e., false positives) once the diagnosis is in widespread use beyond the setting in which it originated.

New diagnoses are usually offered by specialists who have great expertise in a specific area and whose experience is based on highly selected referral patterns to their clinical or research practice. Sets of criteria developed in specialty programs, however, will be used, as all of *DSM-IV* will be used, in widely diverse populations and by much less expert assessors. For example, a new set of criteria for bipolar II disorder would probably identify few false positives if applied by mood disorder experts in a mood disorders clinic. The same set of criteria applied more generally might result in a high number of individuals given inaccurate diagnoses, with significant treatment implications. It is often difficult to discriminate hypomania from brief periods of euthymia in patients with longstanding depressive episodes. This becomes particularly problematic in this diagnostic category, which hinges on the presence of a history of hypomanic episodes.

There are other serious potential costs that accompany increased coverage. The additional explanatory value provided by each new diagnosis must be balanced against the added weight it places on an already quite cumbersome system of classification. New diagnoses that are offered to cover very rare and exotic conditions may add unnecessary complexity to the system for a very low yield in improved coverage. Additional categories cut the diagnostic pie into smaller and smaller pieces, which may create definitional overlap across categories and increase, perhaps inappropriately, levels of comorbidity among near-neighbor categories. When we recognize new disorders that frequently co-occur with other new or existing disorders, we may be reifying as separate entities components of a single complex syndrome.

Some of the proposed diagnostic categories would increase the coverage of the *DSM* system to include conditions which are below the current thresholds set for severity or duration (e.g., minor depression). The thresholds established in *DSM,* however, may not always separate sufferers (those who have impairment or distress) from nonsufferers; that is, "subthreshold" is not the same as "subclinical." Because many individuals struggle with these below-threshold conditions, clinicians and researchers hope to incorporate descriptions of these disorders in the diagnostic nomenclature so as to increase their identification and treatment. Many of these disorders may be more prevalent in the general population; thus, incorporating these categories in the nomenclature would dramatically increase the apparent overall prevalence of mental disorders.

Furthermore, some new and unproven diagnoses may lead to a trivialization of the construct of mental disorders and/or its misuse. All of these concerns are especially troubling if there is a lack of solid evidence that the new diagnoses are useful in predicting prognosis, treatment selection, or outcome.

## ARE NEW DIAGNOSES MEANT TO STIMULATE RESEARCH OR RESULT FROM IT?

An argument that is often advanced for a new diagnosis, particularly one which is supported by very limited evidence, is that its inclusion in *DSM-IV* is necessary to stimulate research in an area which has received insufficient attention. There are several mechanisms through which such stimulation is anticipated. The description of a new diagnosis and provision of a set of criteria make it more likely that this diagnostic area will capture the attention of clinical researchers and assist in the development of instruments which reflect a consensus on ways of making the diagnosis across research programs. There is also the unfortunate presumption that inclusion in *DSM* will increase the credibility of the area for various research funding agencies, pharmaceutical companies, and regulatory agencies. It is often pointed out that *DSM-III* and *DSM-III-R* have been major facilitators of research efforts in a number of areas that might have remained much more obscure and unresearched if they had not been included in the official nomenclature. There are some who maintain that one of the most important goals of *DSM-IV* should be this identification of important new diagnostic questions as a guide to future research efforts.

Balancing these arguments is a concern that including an unproven experimental diagnostic category in *DSM-IV* may confer upon that category an approval which it does not yet merit, with possible negative consequences for clinical practice, research, and educational efforts. Such categories should not be included solely to increase research efforts. Instead, we encourage clinicians and researchers to use the more traditional approach of publishing in peer-reviewed journals as a means of increasing interest in and communication about certain proposed diagnostic categories. It is our sense that research should drive *DSM* and not the other way around. It is much more appropriate to incorporate diagnoses once the need for their inclusion has been well documented in the published literature. Given the current state of research efforts, it no longer makes sense to consider including a diagnostic category in the absence of empirical support, even if a group of clinicians agree that the category might be a useful one. It is impossible to predict in the absence of research how a diagnosis and its criteria will perform.

We have, however, made plans for the development of a *DSM-IV Sourcebook*, which will be published in conjunction with *DSM-IV*. The *DSM-IV Sourcebook* will include summaries of all of the published and unpublished data the work groups have considered in their work on *DSM-IV*. A summary of the data available on each proposed new diagnostic category will be included. The *Sourcebook* will provide a comprehensive compendium of recommendations for needed future research. We are also considering incorporating an appendix in *DSM-IV*, similar in some ways to the appendix included in *DSM-III-R*, for proposed diagnostic categories that are not ultimately included in the body of *DSM-IV*. Such an appendix would include only the proposed diagnostic categories for which a careful literature review has been completed.

## PROBLEMS IN "SUNSETTING" DIAGNOSES

In reaction to the remarkable expansion of new diagnostic categories introduced by *DSM-III* and *DSM-III-R*, the question has been raised whether the same high standards of empirical support required for new diagnoses should also be applied to existing categories. There are clearly categories in *DSM-III-R* which are based on such limited evidence that they would not meet current standards for inclusion. Nonetheless, there are a variety of reasons to demand more support for new than for existing categories. A conservative approach to *DSM-IV*—one that hopes to minimize arbitrary changes based purely on expert consensus—must oppose the removal of existing categories as well as the addition of newly proposed categories in the absence of strong evidence recommending either action. The burden of proof generally rests on providing convincing data for either the removal or the addition of categories in preference to keeping the status quo.

Even with this caveat, there are several diagnoses in *DSM-III-R* for which a review of the evidence may indeed lead to a recommendation that they not be included in *DSM-IV*. For example, several diagnoses in the section on child and adolescent disorders, including identity disorder, overanxious disorder, and avoidant disorder, were included in *DSM-III* with little empirical support and may be better accounted for by other diagnoses in the system. *DSM-III-R* also has several categories of gender dysphoria that may be better organized into one category.

## TOWARD BALANCED SOLUTIONS

*DSM-III* and *DSM-III-R* were inclusive in their attitude toward new diagnoses. Spitzer et al. (2) stated that "one of the guiding principles in the development of *DSM-III* has been an attempt to include in the classification all conditions that a significantly large group of clinicians believe are of clinical importance, providing that the condition can be reliably defined so that it can be distinguished from other conditions." Spitzer et al. (3) further explained that "because the *DSM-III* classification is intended for the entire profession, and because our current knowledge about mental disorder is so limited, the Task Force has chosen to be inclusive rather than exclusive . . . . If there is a general agreement among clinicians, who would be expected to encounter the condition, that there are a significant number of patients who have it and that its identification is important in their clinical work, it is included in the classification." More recently, Kass et al. (4) noted that "it is often necessary to recommend for general use a diagnosis for which only face validity can be demonstrated." The approach used in *DSM-III* and *DSM-III-R* for the consideration of new diagnostic categories was appropriate given the amount of empirical information available at the time in which they were developed. We are fortunate that in the development of *DSM-IV* we are able to draw on a significantly larger pool of information made possible by the publication of *DSM-III* and *DSM-III-R*.

As we have considered the criteria for including diagnostic categories in *DSM-IV,* we have taken into account expressions of concern about the ways in which new diagnoses were incorporated in *DSM-III* and *DSM-III-R.* For example, what constitutes "general agreement" among clinicians has never been particularly clear. Furthermore, the lack of specific information and documentation about the decision-making process and rationale in *DSM-III* or *DSM-III-R* may have given some people the impression that the decisions which were ultimately made were politically rather than empirically driven.

In preparing *DSM-IV,* we will attempt to strike a balance between differing attitudes toward the inclusion of new diagnoses. There are many who will be disappointed when one or another proposed category is not included and who warn us that failing to include this or that particular diagnosis will result in a deficient system which will cripple clinical practice and research efforts. We are also advised, however, that to continue the rush of new diagnoses will undercut the empirical foundations and credibility of the system.

This more conservative viewpoint toward new diagnoses has been most clearly and succinctly articulated by Blashfield et al. (5), who have delineated a series of specific and stringent criteria for the inclusion of new categories. We are in substantial agreement with the spirit of their position but perhaps would be more flexible in applying it. From the outset of the development of *DSM-IV,* we have maintained an ongoing discussion about the criteria that could be applied to making decisions about adding and subtracting categories. In an early *DSM-IV* methods conference, criteria for adding and subtracting diagnoses (E. Frank, presentation at 1988 conference) were discussed in detail. Participants agreed that it was important to have information on how a proposed diagnostic category would facilitate communication, on the category's clinical utility, reliability, and descriptive validity, and on associated external validators. The external validators (K. Kendler, presentation at 1988 conference) to be examined would include antecedent validators (e.g., demographic characteristics, premorbid personality, family history, and precipitating factor), concurrent validators (e.g., biological, physiological, and psychological variables), and predictive validators (e.g., diagnostic consistency, social, occupational, and other follow-up variables, and treatment response). Any proposal for the possible incorporation of an additional diagnostic category would systematically, objectively, and comprehensively review the evidence in the literature on all of these different factors. This process is described in more detail elsewhere (6).

At the same time, there are other important factors and considerations. Given the importance of international communication, new diagnoses that are already included in *ICD-10* will, all other things being equal, have a much better chance of inclusion in *DSM-IV* than will new diagnoses that are not mentioned in *ICD-10.* On the other hand, new diagnoses that are subject to controversy and/or possible misuse will require especially strong empirical support. Insofar as possible, we will attempt to avoid controversies by including only those new diagnoses that command widespread empirical and clinical support. While the major goal of *DSM-IV* is clinical, research, and educational utility, we will be especially cautious about new diagnoses that might be stigmatizing or have an adverse forensic impact. New diagnoses that will dramatically affect the overall prevalence of mental disorders will also be carefully scrutinized.

Before including a suggested new diagnosis, we are attempting to gather empirical data through either field trials or data reanalyses to determine its likely impact. We will determine which existing categories most overlap with the diagnosis in question, and whether the suggested new diagnosis can be better included as a specific example in the "not otherwise specified" category. There are no infallible rules to apply. Ultimately, we must exercise careful clinical judgment and common sense in the context of a comprehensive awareness of the empirical data relevant to a particular issue.

## ILLUSTRATIONS

We have chosen from among the many proposed new diagnoses for *DSM-IV* three different examples. These suggestions provide an opportunity to give concrete examples of the many factors that must be balanced in making these decisions and of the different degrees of evidence available for different categories.

### *Acute Stress Disorder*

A review of the literature has highlighted the possible usefulness of including acute stress disorder (which some have termed "brief reactive dissociative disorder") as a separate and distinct category (7). This diagnostic category would describe the immediate psychological consequences of major stress and might help to fill a nosologic gap between posttraumatic stress disorder and adjustment disorder. Acute stress disorder is currently included in the *ICD-10* diagnostic criteria for research; the diagnosis is given to individuals who have been exposed to an exceptional medical or physical stressor and have experienced the immediate onset of anxious and dissociative symptoms which have abated relatively promptly. One potential adverse consequence of this diagnostic category is that a relatively large proportion of disaster victims would be labeled as having a mental disorder, however transitory and free of stigma it might be. The availability of this diagnosis would be useful in early case finding and preventive efforts.

To learn more about the prevalence, impairment, predictive power, and optimal definition of acute stress disorder, a series of questions has been systematically applied to five different sets of data collected on individuals who have recently experienced man-made or natural disasters. The John D. and Catherine T. MacArthur Foundation has sponsored analyses of these data sets and a number of other analyses of data sets for *DSM-IV*. Evaluating proposed sets of diagnostic criteria against a series of already existing data sets is a novel approach and has been an exciting and important step in the *DSM-IV* process of empirical review. Extensive evidence supporting the existence of acute stress disorder and its inclusion in *ICD-10* make it likely that this diagnostic category will ultimately be incorporated in *DSM-IV*.

### *Mixed Anxiety/Depression and Minor Depression*

A series of literature reviews suggest that individuals are frequently encountered in outpatient, primary care, and community samples who do not meet the full criteria for depression but who do have symptoms of depression, perhaps combined with symptoms of anxiety (8–12). There is evidence that such individuals have a clinically significant level of impairment which is equivalent to that associated with many nonpsychiatric illnesses. The absence of these disorders from the nomenclature may lead to failure to identify people who manifest these syndromes, particularly in outpatient and primary care settings, and consequently to their incomplete diagnosis and treatment. *ICD-10* includes a mixed anxiety/depressive disorder for individuals who fail to meet existing definitions of syndromal levels of either kind of disorder.

It is possible that mixed anxiety/depression and minor depression are highly prevalent. Inclusion of these disorders in the nomenclature, in diagnostic algorithms, and in semistructured interviews might greatly increase the apparent overall prevalence of mood and anxiety disorders, and in turn, of all mental disorders. There is no inherent problem in high prevalences of disorders—witness the high rates of hypercholesterolemia and obesity as these have been generally defined in our population—so long as it is clear that the threshold established is associated with clinically significant distress and/or disability and that the category is useful in predicting prognosis and guiding treatment. There are few data, however, concerning the treatment implications or other validators of mixed anxiety/depression and minor depression. The concern with mixed anxiety/depression and minor depression, then, is that we might create a whole cohort of new patients without sufficient evidence that their identification as patients provides useful information for improving treatment.

To help clarify these issues, we are conducting a field trial to determine the prevalence, impairment, optimal definition, and overlap of mixed anxiety/depression and minor depression in primary care settings. This will also help to settle the question of the degree to which the high prevalence of "subthreshold" patients in primary care is a function of differences in the quality of diagnostic assessment. While the field trial will clarify many questions, a cross-sectional field trial will not be able to provide data on the treatment implications, course, or prognosis for these diagnostic categories. One possible compromise would be a clear description of these syndromes in the "not otherwise specified" text and the presentation of potential sets of criteria in the *DSM-IV Sourcebook* or the appendix to *DSM-IV*.

### *Sadistic Personality Disorder*

Sadistic personality disorder, which was included in the *DSM-III-R* appendix of categories needing further study, is an example of a proposed category that will not be included in *DSM-IV*. A review of both published literature and unpublished findings in this area (13) has uncovered few if any studies on the prevalence, phenomenology, sex bias, descriptive and external validators, and possible misuse of this diagnostic category. One survey of clinicians has suggested that there would be considerable overlap between this category and other axis II categories and that clinicians and researchers would rarely use the category. The lack of any empirical support and historical tradition for this category as well as any compatibility with *ICD-10* makes it impossible to recommend it for inclusion in *DSM-IV*.

## CONCLUSIONS

Modifying the diagnostic manual in any way has tremendous conceptual and practical implications. These implications are magnified when the modifications involve the addition or deletion of whole diagnostic categories. We have tried in this article to share some of these practical and conceptual considerations. The addition or deletion of diagnostic categories reflects our beliefs about what constitutes a mental disorder and how mental disorders can best be organized.

It is to be hoped that future systems, *DSM-V* and beyond, will be based on a much more profound understanding of mental disorders than is currently possible. With the availability of increased knowledge, many of our current diagnostic conventions will undoubtedly become much less pertinent. We can look forward to future diagnostic systems based on pathogenetic understanding, rather than more superficial descriptive similarities, which will be both more elegantly clear and more powerfully predictive. Diagnostic categories will be more specific, better validated, and less heterogeneous. In such an environment, many of the present diagnoses will no doubt be retired as interesting historical relics that reflect our current relatively naive understanding.

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# Abnormal Intracellular Calcium Ion Concentration in Platelets and Lymphocytes of Bipolar Patients

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*The authors measured intracellular $Ca^{2+}$ concentrations in four manic and five bipolar depressed patients and seven comparison subjects. Platelet and lymphocyte intracellular $Ca^{2+}$ concentrations were comparable. The patients' mean intracellular $Ca^{2+}$ concentrations were higher than those of the comparison subjects and demonstrated more interindividual variation. These findings suggest a diffuse abnormality in mechanisms affecting intracellular calcium homeostasis in bipolar disorder.*

(Am J Psychiatry 1992; 149:118–120)

In the last several years there has been interest in the possible role of the membrane phosphatidylinositol (PI) and calcium ion ($Ca^{2+}$) second messengers in bipolar affective disorders. Because increases in free intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) generated by PI turnover and $Ca^{2+}$ influx regulate neuronal function in a manner similar to that of blood platelets (1) and lymphocytes (2), it may be possible to use such cells as markers of changes in the brain. In addition, if hyperactivity of these signaling mechanisms were observed in more than one type of peripheral cell, it might suggest a generalized shift in cellular dynamics that is related to the hyperactive physiology of many bipolar states.

Previous reports suggested higher resting and agonist-stimulated $[Ca^{2+}]_i$ in blood platelets of untreated manic patients (3) and bipolar depressed patients (3, 4) than in comparison subjects. In the present study we used Fura 2, a calcium-chelating fluorescent intracellular $Ca^{2+}$-binding dye, to test the hypothesis that high $[Ca^{2+}]_i$ in lymphocytes could also be demonstrated. A positive result would suggest that patients with mood disorders have an abnormality in $Ca^{2+}$ signaling in two different kinds of cells in which a variety of other abnormalities have been reported.

## METHOD

### *Subjects*

Nine normotensive bipolar patients and seven comparison subjects participated in the study. Informed consent was obtained from all subjects. The nine bipolar patients had not received treatment or used alcohol or street drugs for at least 3 months. Four had current episodes of mania (two men and two women; mean age=32.8 years, range=21–45 years), and five had depression with past histories of mania (two men and three women; mean age=37.3 years, range=25–48 years). We compared these patients with seven normotensive subjects without personal histories of psychiatric disorders or first-degree relatives with such histories (five men and two women; mean age=36.4 years, range=22–50 years). The patients were diagnosed according to *DSM-III-R* criteria by means of semistructured interviews given by two experienced clinicians (S.L.D. and M.T.).

### *Procedure*

The measurements were all made during the same time of year. At 9:00 a.m. 80–100 ml of blood was

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drawn into 1/6 volume acid citrate dextrose anticoagulant containing 100 μM of aspirin, and it was prepared as described previously (3, 4). Briefly, centrifugation of platelet-rich plasma yielded platelet-poor plasma and a platelet pellet that was resuspended in Ringer's citrate buffer with apyrase. The suspension was centrifuged for 10 minutes at 570 *g*, and the platelets ($0.5\times10^9$ cells/liter) were resuspended in HEPES buffer with EGTA and $CaCl_2$ (final $[Ca^{2+}]_i$=1.0 mM). Aliquots of 1.2 ml were incubated with either 1 μM of Fura 2-acetoxymethyl ester (Fura 2-AM) or, to measure cell autofluorescence, an equivalent volume of dimethylsulfoxide (DMSO).

To the platelet-poor plasma was added 6% dextran (molecular weight=500,000), and the volume was adjusted to 50 ml with 0.9% saline. After erythrocyte sedimentation, leukocyte-rich plasma was centrifuged at 275 *g* for 6 minutes. The pellet was resuspended in 2 ml of platelet-poor plasma per 50 cc of original blood and underlayed in polypropylene tubes first with 42% and then with 51% Percoll in platelet-poor plasma. After centrifugation for 11 minutes at 275 *g*, mononuclear cells were removed, washed once in platelet-poor plasma, resuspended in the HEPES medium, and placed in tissue culture plates to remove monocytes. Lymphocyte concentration was adjusted to $1\times10^9$ cells/liter of HEPES. Aliquots of 1.2 ml were then incubated for 60 minutes with either Fura 2-AM or DMSO as already described.

After incubation with Fura 2-AM, platelets and lymphocytes in random order were re-pelleted to remove external dye and resuspended in the HEPES medium. Fluorescence was measured at 37 °C on a Perkin Elmer LS5B fluorimeter by using excitation wavelengths of 340 and 380 nm and an emission wavelength of 498 nm. After subtracting cell autofluorescence and manganese quench of fluorescence from the Fura 2 that leaked out of the cell and bound $Ca^{2+}$ in the medium, we calculated $[Ca^{2+}]_i$ according to the method of Grynkiewicz et al. (3–5). Determinations were usually performed in duplicate, and the mean value was used. The interassay variability was <5% to 7%.

### *Statistical Analysis*

Using the SAS-PROC GLM computer program, we conducted a repeated measures analysis of variance with cell type (platelet, lymphocyte) as the repeated factor and diagnostic group (comparison, bipolar) as the fixed effect. Interindividual variations in $[Ca^{2+}]_i$ in the bipolar patients and comparison subjects were compared by determining F ratios of the two groups' standard deviations for $[Ca^{2+}]_i$ in platelets and $[Ca^{2+}]_i$ in lymphocytes.

## RESULTS

**TABLE 1. Intracellular Calcium Ion Concentrations in Lymphocytes and Platelets of Bipolar Patients and Comparison Subjects**

| | Intracellular $Ca^{2+}$ Concentration (nM) | |
|---|---|---|
| Subject | Platelet | Lymphocyte |
| Bipolar patients | | |
| 1 | 103 | 104 |
| 2 | 118 | 122 |
| 3 | 160 | 147 |
| 4 | 97 | 102 |
| 5 | 141 | 193 |
| 6 | 104 | 99 |
| 7 | 152 | 159 |
| 8 | 112 | 129 |
| 9 | 102 | 103 |
| Mean | 121 | 129 |
| SD | 23.8 | 32.2 |
| Comparison subjects | | |
| 1 | 84 | 84 |
| 2 | 83 | 93 |
| 3 | 79 | 82 |
| 4 | 83 | 86 |
| 5 | 88 | 88 |
| 6 | 71 | 69 |
| 7 | 63 | 77 |
| Mean | 79 | 83 |
| SD | 8.7 | 7.8 |

As shown in table 1, there was no significant interaction between group and cell type (F=0.25, df=1, 14, p≤0.62) (i.e., no significant difference between platelet and lymphocyte $[Ca^{2+}]_i$ in the comparison subjects and bipolar patients) and no significant difference between platelet and lymphocyte $[Ca^{2+}]_i$ (F=2.54, df=1, 14, p≤0.13). The platelet and lymphocyte $[Ca^{2+}]_i$ values were nearly identical in most individuals, supporting the reliability of the assay. On the other hand, there was a large and significant difference between the comparison and bipolar subjects (F=17.69, df=1, 14, p≤0.0009); $Ca^{2+}{}_i$ in both platelets and lymphocytes was on average 1.5 times as high in the bipolar subjects as in the comparison subjects. Every $[Ca^{2+}]_i$ measure for the individual bipolar patients was more than two standard deviations above the mean for the comparison subjects. There was greater interindividual variation of $[Ca^{2+}]_i$ in the patients than in the comparison subjects for both platelets (F=7.48, df=8, 6, p≤0.03) and lymphocytes (F=17.04, df=8, 6, p≤0.005).

## DISCUSSION

The finding of higher lymphocyte $[Ca^{2+}]_i$ in bipolar patients than in healthy subjects extends previous findings about $[Ca^{2+}]_i$ in platelets (3, 4) and raises several new issues. First, it may now be appropriate for investigators in other laboratories to attempt replication with either type of cell. In view of the greater heterogeneity of lymphocyte and platelet $[Ca^{2+}]_i$ in bipolar patients, which probably reflects their clinical and possibly genetic heterogeneity, some populations may be more likely to demonstrate this abnormality than others. Second, similar hyperactivity of the intracellular $Ca^{2+}$ signal in unrelated peripheral cells could imply a generalized abnormality of the cell membrane, a G-protein, or other mechanism of intracellular $Ca^{2+}$ homeostasis in bipolar illness that could extend to brain neurons. In contrast, a study of hypertensive subjects (6) showed high $[Ca^{2+}]_i$ in platelets but not lymphocytes, suggesting a more circumscribed abnormality, perhaps related only to vasomotor instability.

Another implication is that impairment of various in vitro aspects of lymphocyte mitogenesis and cytotoxicity that have been reported in depression (7) and mania (Z. Kronfol and J.D. House, unpublished data, 1989) could be related to an abnormality of intracellular $Ca^{2+}$ signaling. Although a moderate increase in $[Ca^{2+}]_i$ initiates lymphocyte proliferation (8), excessive increases can directly inhibit lymphocyte activity (9). Elevated resting $[Ca^{2+}]_i$ could also impair lymphocyte function by activating a $Ca^{2+}$/calmodulin-dependent phosphodiesterase not normally present in the quiescent state that inhibits further cellular activity by hydrolyzing cyclic nucleotides (8). Increased activation of suppressor T cells by a heightened intracellular $Ca^{2+}$ signal is another possible mechanism of reduction of the overall lymphocyte response.

Caution is necessary, however, in drawing such conclusions. We did not measure lymphocyte function and therefore cannot correlate this with $[Ca^{2+}]_i$. In addition, the hyperactive $Ca^{2+}$ signal may be derived from a subgroup of lymphocytes and have limited implications for the entire population of cells. Although our patients were free of medication and other substances long enough for a new generation of platelets and lymphocytes to have been formed, it is also conceivable that previous experience with these or other substances could somehow have affected stem cells. A more relevant concern is that high $[Ca^{2+}]_i$ could be a marker of severity or some other clinical characteristic, rather than bipolarity. Further studies might address these issues by correlating $[Ca^{2+}]_i$ in lymphocyte subpopulations with discrete measures of lymphocyte function in patients in whom severity, episode frequency, and other potentially relevant clinical factors are controlled.

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# Verapamil Versus Lithium in Acute Mania

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*Twenty acutely manic patients were studied in a double-blind randomized trial comparing verapamil with lithium. The Petterson Mania Scale, the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impression (CGI) were administered before treatment and weekly during 4 weeks of treatment to evaluate response to verapamil and lithium. Both treatment groups improved significantly, and there were no significant overall differences between treatments.*

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Lithium is the standard treatment for acute manic episodes, but 20%–40% of patients do not respond well, and side effects impair many patients (1). Lithium may affect calcium metabolism, and patients with bipolar disorder may have abnormalities in calcium metabolism as a characteristic of this disorder (2). The efficacy of verapamil in the treatment of mania has been examined in several small open studies and one double-blind study involving fewer than 10 patients (3, 4).

## METHOD

This study was conducted at a 250-bed hospital. Included were newly hospitalized patients meeting *DSM-III-R* criteria for an acute manic episode. Pregnant women were excluded, as were patients in whom verapamil or lithium was contraindicated. Also excluded were patients treated recently with depot neuroleptics. Patients were evaluated with the Clinical Global Impression (CGI) (5), the Petterson Mania Scale (6), and the Brief Psychiatric Rating Scale (BPRS) (7) before treatment (baseline) and weekly for 4 weeks of treatment.

Twelve patients who were given verapamil finished the protocol; there were four men and eight women in this group, and their median age was 33 years. Eight patients who were given lithium finished the protocol; there was one man and seven women in this group; their median age was 34.

Medications were packaged as identical-appearing capsules containing 80 mg of verapamil or 300 mg of lithium carbonate. Verapamil doses were titrated from 80 mg b.i.d. the first day, 80 mg t.i.d. for the next 2 days, and then 80 mg q.i.d. for the remainder of the study. The initial lithium dose was 0.5 meq/kg; subsequent doses were adjusted to maintain blood levels in the range of 0.75 to 1.5 meq/liter.

The study medications were packaged and dispensed by a pharmacist according to a randomization list maintained in the pharmacy. One physician managed clinical care and monitored lithium blood levels, ensuring that the blind rater (E.S.G-T.) had access to no information that could lead to identification of the treatment.

## RESULTS

Unadjusted mean Petterson Mania Scale scores and CGI severity scores at baseline and covariance-adjusted mean scores for the 4 weeks of drug treatment are presented in table 1. With the exception of pretreatment values, the standard deviations in each section of the table are square roots of the error mean squares from the analysis of covariance (ANCOVA). These are provided because raw standard deviations do not convey the appropriate error variability for comparison of means after correction for baseline differences (8, 9).

Patients assigned to the verapamil group were more disturbed at baseline than were patients in the lithium group. Primary analyses were therefore baseline-covaried ANCOVA. Both groups improved significantly on the four measures ($p<0.01$). The groups did not differ significantly in the magnitude of treatment-induced change. We also analyzed the change in scores before and after treatment in addition to ANCOVA-adjusted measures. Even though those results should reflect in part the significant or near significant baseline differences in this randomized study, none of the simple com-

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**TABLE 1. Scores on the Petterson Mania Scale and the CGI for Acutely Manic Patients Given Verapamil or Lithium**

| Test and Time | Mean Score: Patients Given Verapamil (N=12)[a] | Mean Score: Patients Given Lithium (N=8)[a] | p | SD[b] |
|---|---|---|---|---|
| Petterson Mania Scale[c] | | | | |
| Before treatment | 23.92 | 20.38 | 0.08 | 4.23 |
| Week 1 | 19.25 | 18.87 | 0.82 | 3.20 |
| Week 2 | 17.29 | 16.75 | 0.90 | 5.09 |
| Week 3 | 14.75 | 16.12 | 0.47 | 3.72 |
| Week 4 | 13.29 | 12.39 | 0.30 | 2.97 |
| CGI severity score[d] | | | | |
| Before treatment | 5.33 | 4.38 | 0.03 | 0.90 |
| Week 1 | 4.49 | 4.14 | 0.21 | 0.51 |
| Week 2 | 4.07 | 4.28 | 0.65 | 0.87 |
| Week 3 | 3.91 | 3.64 | 0.53 | 0.81 |
| Week 4 | 3.53 | 2.96 | 0.34 | 1.27 |

[a] The means for the baseline values are raw means; the means for the treatment weeks are adjusted for covariance.

[b] With the exception of pretreatment values, the standard deviations are square roots of the error mean squares from the analysis of covariance.

[c] Difference across weeks: drugs, p=0.89; pattern, p=0.38.

[d] Difference across weeks: drugs, p=0.48; pattern, p=0.57.

parisons of changes in scores before and after treatment approached statistical significance (p<0.20).

In a repeated measures design, reliability in discriminating differences within patients over time and reliability in discriminating true differences between patients in a cross-section of time are important. A pooled within-patient correlation matrix with communality estimates in its diagonal was subjected to a principal axes factor analysis, and squared loadings on the first common factor of the 4×4 within-patient correlation matrix were calculated as lower bound reliability estimates. A similar procedure was used to discriminate between individuals with different levels of global severity in a cross-section of time. A pooled within-weeks correlation matrix was calculated by combining the covariances among the four measures calculated across patients separately for each week. The within-patient reliability estimates for the Petterson Mania Scale, BPRS, and CGI severity scores were 0.74, 0.61, and 0.72, respectively. The between-patient reliability estimates were 0.62 (Petterson Mania Scale), 0.70 (BPRS total score), and 0.77 (CGI severity).

The two groups were comparable in terms of number of side effects. One patient in the verapamil treatment group developed constipation, and two patients in the lithium treatment group suffered nausea and vomiting. Three initially randomized patients were dropped from the lithium protocol: one because of cardiotoxicity and another because of assaultive behavior. The third lithium patient withdrew voluntarily, accounting for the reduced size of that group. More patients in the verapamil group received a combination of 5 mg of haloperidol and 2–4 mg of lorazepam for optimal control of excessive agitation (10). Seven patients out of 12 in the verapamil group and four of the eight lithium patients received a combination of haloperidol and lorazepam for control of excessive agitation. Three of the verapamil patients accounted for most of the neuroleptic-hypnotic use.

## DISCUSSION

The difference between treatment groups that was present at baseline in spite of random assignment complicates interpretation of differences in treatment effects. If one examines unadjusted raw scores (not shown), the verapamil group evidenced greater absolute change from baseline to endpoint. If one examines the covariance-adjusted means (table 1), the trend in symptom reduction across weeks favors lithium over verapamil. However, there was no statistically significant difference between the groups in either case, and both treatment groups improved significantly. In spite of the absence of a placebo control group in this study, the rate of symptom reduction in both treatment groups is indicative of a treatment effect. On this basis, we conclude that the results add to the evidence that verapamil is effective in treating some patients with manic conditions. Larger studies should be undertaken to determine whether verapamil may be effective in patients who fail to respond well to lithium.

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# What Is Meant by the Term "Binge"?

**Sarah J. Beglin, M.A., and Christopher G. Fairburn, D.M.**

*Systematic examination of the use of the word "binge" by 243 young women revealed discrepancies between the lay and technical uses of the term; the young women placed great emphasis on loss of control and less on the quantity eaten. These discrepancies indicate that the term "binge" should be clearly defined in clinical practice.*

(Am J Psychiatry 1992; 149:123–124)

In view of the high prevalence of eating disorders among young women in general, and among young female psychiatric patients in particular, female patients in this age group need to be asked as a matter of routine about binge eating. For this reason the term "binge" must be included in every psychiatrist's lexicon.

Like many technical terms in psychiatry, the word "binge" is also in general use. This dual use is a potential source of confusion. The focus of this paper is on the use of the word "binge" by young women in the community. Such use needs to be understood if responses to questions about binge eating are to be interpreted correctly. We conducted two studies. The aim of the main study was to examine how young women apply the term to their own eating. The aim of the supplementary study was to determine what young women understand the term to mean.

## METHOD

The source sample consisted of 285 women, aged 16 to 35 years, who were selected at random from the case registers of two family practices. One practice was in a suburban area, and the other served a rural population. Of the 285 subjects, 243 (85%) agreed to take part. Their mean±SD age was 26.6±5.5 years. Sixty percent were married, and 4% were separated or divorced. The social class distribution was as follows: 3% in class I, 26% in class II, 44% in class III, 13% in class IV, and 3% in class V; 8% were full-time students, and the class of 3% was unknown.

Subjects who agreed to take part underwent a research interview that included the Eating Disorder Examination, a widely used measure of the eating habits and attitudes characteristic of people with eating disorders (1). The Eating Disorder Examination distinguishes four forms of overeating: objective bulimic episodes, subjective bulimic episodes, episodes of objective overeating, and episodes of subjective overeating. These are mutually exclusive, although it is not uncommon for subjects to report episodes of more than one type. The distinction between the four types is based on the presence or absence of two features, loss of control during the episode (required for both types of bulimic episode) and the consumption of a large amount of food (required for objective bulimic episodes and episodes of objective overeating). Loss of control is considered present if the subject would have had difficulty either in preventing the episode of overeating from starting or in stopping it once it had started. The amount eaten is considered large when it clearly exceeds the quantity that would usually be eaten under the circumstances.

For the purpose of the present study, questions about the term "binge eating" were added to the Eating Disorder Examination. Subjects who had experienced recent episodes of overeating were asked to specify which they considered to be binges. In this way it was possible to add individual subjects' use of this term to the classification provided by the Eating Disorder Examination.

A small supplementary study was conducted to shed light on the use of the term "binge." The subjects were a subset (N=40) of the entire sample of 243 women. They did not differ from the remainder in their demographic or clinical features. Each of these women was first asked what she understood by the term "binge," and her answers were classified on the basis of the presence or absence of 11 features said to characterize

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binges. Then, each one of the 11 features was reviewed and the subject was asked if it was, or was not, characteristic of binges.

## RESULTS

Many of the 243 subjects reported recent episodes of overeating. Over the preceding 28 days, 22 (9%) had experienced objective bulimic episodes, 47 (19%) had had episodes of objective overeating, 19 (8%) had had subjective bulimic episodes, and 107 (44%) had had episodes of subjective overeating. The proportions of the episodes of these four forms of overeating that the subjects classified as binges were as follows: objective bulimic episodes, 83%; episodes of objective overeating, 19%; subjective bulimic episodes, 42%; and episodes of subjective overeating, 13%. Thus, few of the episodes of objective overeating were classified as binges, despite the large amount of food eaten, whereas nearly one-half of the subjective bulimic episodes were so classified, even though the amount eaten could not be regarded as large. This indicates that the subjects placed great emphasis on loss of control (as defined by the Eating Disorder Examination) and less on the quantity eaten.

In the supplementary study, when the subjects were not prompted, the only feature on which there was consensus was that a binge involves the consumption of a large amount of food. When prompted, most subjects had definite opinions on which of the 11 features characterize a binge, but this certainty was associated with little agreement on the features themselves. There were four exceptions. At least three-quarters of the subjects thought that the following features are required for episodes of eating to be classified as binges: eating a large amount of food (N=37, 93%), extreme fullness (N=33, 83%), a sense of loss of control (N=36, 90%), and subsequent dysphoric mood (N=30, 75%).

## DISCUSSION

The definition of "binge" has changed since its original inclusion in *DSM-III*. There the definition was "rapid consumption of a large amount of food in a discrete period of time, usually less than two hours." In *DSM-III-R*, the suggested 2-hour limit was dropped. In the provisional *DSM-IV* scheme, a more radical change is proposed: loss of control is required (2). The provisional definition is as follows:

> An episode of binge eating is characterized by both:
> i. eating, in a discrete period of time (e.g., in any two-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time; and,
> ii. a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

This is essentially the definition of an objective bulimic episode used in the Eating Disorder Examination.

Our two studies allowed a comparison of the technical use of the term "binge" with the definition used by a community sample of young adult women. When the young women were asked to apply the term to their own behavior, it emerged that they placed great emphasis on loss of control and somewhat less on the quantity of food eaten. The former use is in line with the provisional *DSM-IV* definition, but the latter is not.

The findings of the supplementary study suggest that when young women are asked on self-report questionnaires about binge eating (undefined), their responses simply refer to episodes of perceived overeating. However, further questioning of our subjects revealed that binge eating was regarded as a particular form of overeating, in which a large amount of food is eaten with a sense of loss of control and subsequent fullness and dysphoria.

Our subjects were young women in England, and one may therefore ask whether similar findings would have emerged had the study taken place in the United States. However, even if the study had used a North American sample, questions would arise about the generalizability of the findings, since there may well be regional and subcultural differences in the use of the term. The point at issue is not the identification of exactly how the word "binge" is used within a particular subgroup but rather the demonstration, with a relevant sample, that there are discrepancies between the lay and technical uses of the term.

The implication of the findings for clinical practice and research is clear. When the term "binge" is used in a professional context, a clear, unambiguous definition must be provided.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

### GENDER ISSUES

**Women's Progress: Promises and Problems,** *edited by Jeanne Spurlock, M.D., and Carolyn B. Robinowitz, M.D. New York, Plenum, 1990, 258 pp., $39.50.*

This multiauthored book is one of a series entitled Women in Context: Development and Stresses. Each volume is edited by well-respected women academics. As each book appears, it begins to fill the void in authoritative literature on contemporary women's development and experience.

This particular book's focus is mainly on aspects of mothering, although the focus is unstated and several chapters seem not to belong to the mothering theme.

The first chapter, by Adams and Adams, examines family structures and the definition of "family" in different historical periods. It is important to recognize that this definition is fluid and that obstacles to the autonomy of women, erected to preserve "family" values, may come from idiosyncratic views of what a family is.

Spurlock's chapter on singleness touches only briefly on the plight of the single mother; rather, it addresses the myths surrounding women who do not marry. An interesting chapter on foster families highlights the fact that the mothering role is more difficult and less rewarding for foster mothers than it is for the majority of women.

Rogoff-Thompson and Thompson discuss the changing face of adoption in the United States, emphasizing the underlying theme of loss. Birth parents lose a child through adoption; adoptive parents lose the dream of a child born of them. Both sets of parents go through a process of grief and adaptation. Kim adds a chapter on transcultural and transracial adoption, an increasingly prevalent phenomenon. Few longitudinal studies are available to compare the development of transculturally or transracially adopted children with more conventionally adopted children.

Ruth Fuller addresses the problems of working mothers, who currently account for more than half of all mothers. She cites a 1988 review which concluded that maternal employment per se is not significantly related to children's development.

Two chapters discuss the special problems of mothers of disabled children. The personal account of Mary Akerley is particularly informative. There is also an important chapter on mothers who abuse their children, which concludes that the profile of the abusing mother remains poorly articulated.

Three chapters on women offenders, battered women, and homeless women are only peripherally connected to the mothering theme, although crucial to women's experience. Hutchinson's paper on battered women asserts that "pregnancy seems to unleash the deepest and most intense antifemale feelings that the man has." She goes on to delineate specific recommendations for intervention strategies with battered women.

The final chapter is on transsexualism and the female transsexual, an issue that seems out of keeping with the rest of the volume. On the other hand, a chapter by Kirkpatrick on homosexuality and parenting is scholarly, important, and relevant. Between 200,000 and 3,000,000 children in the United States are being brought up by lesbian mothers. For these women, motherhood is the most salient feature of their self-concept. With respect to outcome of lesbian child rearing, comparison studies appear to indicate that the presence or absence of a second adult who is available to the child is the most significant determinant of outcome. Coupled mothers, lesbian or heterosexual, seem to respond to children's needs more readily than do single mothers. This hypothesis needs repeated testing, but the preliminary results presented by Kirkpatrick are important.

In summary, this book provides a new synthesis of contemporary findings about women in different family configurations and reflects on the challenges and determinants of effective mothering. Insofar as some of the chapters do not adhere to this major theme, the book reads somewhat disjointedly and disappointingly.

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**Feminism and Psychoanalytic Theory,** *by Nancy J. Chodorow. New Haven, Conn., Yale University Press, 1989, 273 pp., $25.00.*

This volume represents a synthesis of Nancy Chodorow's thinking as it has evolved from the early 1970s until today. Chodorow traces her early feminist origins and her evolving interest in psychoanalysis, citing the influences of psychoanalysts like Horney, Klein, Mahler, Winnicott, and Loewald.

As a psychoanalytic feminist, Chodorow offers an incisive critique and a penetrating analysis of this perspective. She also acknowledges that "psychoanalytic feminism has not been especially attuned to differences among women—to class, racial, and ethnic variations in experience, identity, or location in social practices and relations" (p. 4).

Her thinking about the etiology of male dominance has shifted over the years from the view that women's mothering was the cause of male dominance to an understanding of it as a complex and multidetermined phenomenon, varying with psychological, cultural, and social constructions of gender. She does indicate, however, that the experience of the powerful mother is a core factor in "the virulence of masculine anger, fear, and resentment of women, or of aggression toward them" (p. 6). Although she does not negate the powerful influence of the father on psychological development, she does not believe that he is the predominant influence.

From a theoretical perspective, Chodorow also focuses on the importance of the development of the self as it differs for men and women. In her conceptualization of object relations, she adds complexity to the feminist view of gender.

The first section of the book consists of four essays from the early- to the mid-1970s under the title The Significance of

Women's Mothering for Gender Personality and Gender Relations. In this section, Chodorow develops her thinking about the significance of women's mothering, describing mother-daughter and mother-son relationships and the impact of mothering on feelings about women and men. She considers the socialization of males and females from a cross-cultural perspective. She argues that through their relationship to their mother, women develop what is called a self-in-relation and men a self that, she states, denies relatedness.

The second section of the book, entitled Gender, Self, and Social Theory, draws on object relations theory and looks at the qualities of self that may be not gender-related. Chodorow also examines and critiques the psychoanalytic sociologists Marcuse and Brown.

In the final section of the book, Psychoanalysis, Psychoanalysts, and Feminism, Chodorow describes psychoanalytic feminism from a number of perspectives, culminating in an essay entitled "Seventies Questions for Thirties Women: Gender and Generation in the Study of Early Women Psychoanalysts." In this she reports her interviews of early women psychoanalysts, trained between the 1920s and early 1940s, whom she interviewed in the early 1980s. These women reveal less gender orientation in their direct responses than they did in the lives they led. They did not see gender as a particularly salient variable, nor did they think they were challenging basic notions of women's nature in their quest for psychoanalytic careers, despite prevailing theoretical perspectives that would have suggested different lives for them.

In this rich and varied but intense and tightly reasoned volume, Chodorow brings us up-to-date on a range of contemporary psychoanalytic thinking in an area that is often not so available in the psychoanalytic literature. Her carefully constructed arguments define the subject and explicate her point of view, but she is not so tightly bound to one theoretical posture that she cannot attend to others. The book is a substantial work, to be read carefully by those interested in psychoanalytic thinking and practice.

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**Making a Difference: Psychology and the Construction of Gender,** *edited by Rachel T. Hare-Mustin and Jeanne Marecek. New Haven, Conn., Yale University Press, 1990, 201 pp., $18.95.*

The difference in the title of this book refers to gender. The difference is twofold. The anatomical-biological difference is relatively fixed, but the meaning and representation of gender is subject to psychological and sociological influence. The social roles of men and women and the expectations of them are affected by cultural attitudes. There are roughly two approaches to the issue. One emphasizes the differences between male and female; the other tends to minimize it. Although each position, in the extreme, is fallacious, both have fostered the examination of the meaning attributed to sexual and gender differences by highlighting the issues. The stereotypes associated with maleness and femaleness abound in paradox and contradiction. The stereotypes are permeated with the implication that maleness is superior to femaleness. Even admirable characteristics that are considered feminine, like nurturance, caring, and intuitiveness, are denigrated in favor of the masculine traits of competitiveness, rationality, and assertiveness.

A major focus in feminist psychology has been the elucidation of the differences between males and females. The authors in this book point out that many studies purported to define maleness and femaleness are flawed by gender bias. The studies of sex and gender differences have been inconsistent and unreliable or have been merely descriptive and nonexplanatory, implying a nonmodifiable trait view of behavior, assuming a fixed definition of sex and gender, and disregarding the varieties in meaning associated with levels of organization from the anatomical to the sociological. Attitudes and behaviors associated with maleness and femaleness are not determined by sex alone but are influenced by the complexity of experiences and psychological organization. Both individual and social issues have to be considered.

This book reveals that, instead of focusing on the explication of gender differences, modern feminist researchers and scholars are concerned with the effect on thought and behavior of prevailing assumptions about sex. Definition of sex is a method of categorizing and communicating expectations. The concept of androgyny has been posited as a corrective to the biases that purport to distinguish males and females from each other. Since the concept of androgyny implicitly assumes male and female characteristics as it considers their blending, it does not resolve the dilemma of gender differences, nor does it enhance our understanding of the meaning of gender.

Knowledge does not exist in a vacuum. It is influenced by prevailing cultural modes. In a male-dominated society like ours, concepts congruent with a masculine outlook prevail while issues like relationships, connectedness, and concern with reproduction are considered feminine and are relatively ignored. Parallel with the questions raised about these issues are recent epistemological concerns that impinge on feminist thinking. Among these is the recognition that truth is not absolute and immutable but is contingent on social relations, historical context, and the knower's interests. Criteria of knowledge are not fixed and are multidetermined.

The further development of feminine psychology depends on the recognition that the influences on the development of sexuality in all individuals are diverse, that sexual attitudes are ill-defined and not fixed, and that attributes of what are considered maleness and femaleness are manifested in both sexes. The task of psychological research and study is to delineate the factors that influence this development and the manifestations of these attitudes and behaviors. Although this book is a very helpful guide to the pitfalls to avoid and the directions in which to proceed in the consideration of sexuality, its comprehensiveness would have been enhanced by more consideration of intrapsychic factors involved in the determination of sexuality.

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**Men and Divorce,** *by Michael F. Myers, M.D. New York, Guilford Press, 1989, 286 pp., $30.00.*

This clinically useful book is the extract of the author's many years of experience in the field of marriage and divorce. Contemporary U.S. society has witnessed increasing dissolution of marriages in recent years. Consequently, there is a need for a better understanding of the impact of separation on the family. In this work, Dr. Myers examines men's experience of the divorce process. His eclectic approach to this task is reflected throughout the book and provides a rich understanding of and a balanced focus on intrapsychic and interpersonal dynamics.

The author's primary goal is to point out that men frequently have difficulty coping with separation. Because they do not directly ask for help, they may express their pain behind a masquerade of self-reliance through somatic problems, alcohol abuse, overwork, and criminal behavior.

*Men and Divorce* is divided into three sections. The first is an overview of historical considerations in marriage and divorce, which sets the stage for the second section, a detailed analysis of different clinical presentations of divorcing men. The third is devoted to therapeutic considerations.

After making a distinction between physical and emotional separations, Dr. Myers critically explores the dynamics underlying the experiences of emotional separation. He tactfully differentiates those separations which are initiated by the husband, those initiated by the wife, and those mutually agreed on because the dynamics and symptoms involved with each may be very different. For example, some men may become involved in several shallow relationships after their wives have initiated separation. This may reflect a defense against intimacy and loss. The true mourning may not actually begin until several months after the physical separation.

Dr. Myers looks at the common experience of many men of finding themselves in the process of separation in a paralyzed position despite their inner conviction that their marriage is over.

Issues related to newly separated men, such as mourning of their lost marriage and adaptation to a new life style, are discussed. The effects of personality, ethnicity, age, and length of marriage on the experience of separation are explored.

Dr. Myers postulates that criminal behavior of abandoned husbands may be triggered in part by the "overwhelming subjective sense of abandonment." Furthermore, he describes the coping strategies of divorcing men with different personality styles, such as overaggressive, passive-aggressive, and passive-dependent.

Other topics discussed are the unique circumstances of divorcing men who are coming out as gay and issues related to divorced fathers and their children.

The last section focuses on treatment strategies and different modes of psychotherapy. These include supportive, behavioral, and insight-oriented approaches. Common themes encountered in treatment, such as anger, dependency, control, grief, male inexpressiveness, loneliness, and isolation, are examined.

The text is easy to read and relatively jargon free, with the added convenience of a brief summary at the end of each chapter. There is also a reference index and a subject index.

This book would appeal as an introductory volume to a broad range of mental health practitioners who work in individual and couples therapy.

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## CARING FOR PATIENTS

**Educating Competent and Humane Physicians,** *edited by Hugh C. Hendrie and Camille Lloyd. Bloomington, Indiana University Press, 1990, 240 pp., $29.95.*

One of the special pleasures of reviewing books for the *Journal* is the sensitivity with which the Book Forum Editor selects books that call on the special areas of interest and expertise of a particular reviewer. On occasion, I feel as if I could accuse her of reading my mind and knowing what seems to be of particular concern to me when she forwards a book.

I have been thinking a great deal about the education of competent, compassionate, and humane physicians who understand the new technologies but retain the caring attitudes of past generations. Because of the current economic climate, the need to see many patients quickly, and concern about managed care, it appears as if several factors are converging to discourage young physicians from caring about their patients as complete human beings and to encourage them, instead, to focus their treatment efforts on specific parts of the body.

Drs. Hendrie and Lloyd have edited a volume whose purpose is to address issues of medical education, particularly the necessity for continuing our efforts to train physicians to be professionally competent and yet maintain the personal qualities required to practice comprehensive and humane health care. The book is dedicated to the memory of Dr. Nancy Roeske, Professor of Psychiatry at Indiana University School of Medicine, who died in April 1986. Dr. Roeske was concerned throughout her distinguished professional career about the socialization process of the health professional and the appropriate environment for medical education. Many of the authors in this book were personal friends of Dr. Roeske and share their memories of her with their academic discourses about today's climate of medicine. I, too, counted Nancy among my mentors and friends and was deeply saddened by her untimely death.

The book is divided into four sections. Part one deals for the most part with literature reviews emphasizing the importance of social factors in understanding the pathogenesis of disease and illness behavior and the critical nature of such an understanding in treating patients. In part two the current functioning of medical school settings is reviewed with respect to the current atmosphere, specifically, selection of medical students and training of medical students and residents, with special attention paid to the development of humanistic qualities.

Part three highlights vital programs designed to sensitize physicians in training to the human and humane aspects of medical practice. Particularly interesting in this section is a historical chapter that describes the nineteenth-century women's medical colleges and the efforts of early prominent women physicians to add humaneness and caring to the technological aspects of medical training. This chapter previews current concerns of education in relation to the loss of caring as technology increases and is especially important for psychiatric educators.

In the final section of the book, René Fox, a colleague and friend of Dr. Roeske, echoes some of the themes of previous chapters in a lecture entitled "Training in Caring Competence: The Perennial Problem in North American Medical Education," which she delivered at the Sister Margaret Hospital in Toronto in March 1989.

Throughout the book, as the authors view historical aspects of this problem, they all share a common concern that physicians in the twentieth century improved their technological skills but might have lost their empathic and humanistic skills—that as the science of medicine progresses the art is lost. These authors also note that despite the fact that consciousness has been raised and solutions proposed, the current crop of medical students continues to be woefully deficient in the ability to be compassionate and to understand and integrate biopsychosocial aspects of medical care. They comment that this deficit contributes to the increase in malpractice suits, the public perception of the physician as greedy, and the lack of trust that impedes recovery, even when the technological aspects of medical care are superb.

I was particularly impressed by the chapter by Dr. Roger Bulger, "The Impact of the Educational System on the Development of the Modern Hippocrates." Dr. Bulger makes clear his own biases about the effects of the educational process on the learner. First, he feels that the educational environment is important to the outcome of education. It does matter to the student how people, data, and resources are to be treated. Second, he says that what we do not know far exceeds what we do know, and that a great deal of what we think we know will be shown to be incorrect in the years ahead. Therefore, integrity and humility ought to be encouraged. Third, he feels that the role model of the teacher is far more important than most teachers seem to appreciate and that the analogy between the student-teacher relationship and patient-physician relationship is not lost on students.

Dr. Bulger discusses factors that have led to a deterioration in the student-teacher relationship, including superspecialization, the big business aspects of clinical departments in medical school, and lack of interprofessional education. He concludes his chapter by suggesting, "Paradoxically, if medicine loses some of its lofty financial and social status, it might turn out that those best suited to meet the care needs of our society would continue to seek out places in the profession and to gain entry to our schools." He reminds the reader that in England, despite physicians' overcrowded offices, patients do not feel a loss in quality of care or commitment among physicians. In the United States, perhaps, a smaller, tighter, but more committed army of healers might emerge side-by-side with the scientists and technicians required to manage our extraordinary diagnostic and therapeutic interventions.

*Educating Competent and Humane Physicians* does not propose any sweeping solutions to a very basic and persistent problem in medical education. However, despite the fact that no ultimate solutions are proposed, any thoughtful educator will know that the authors have shared their thoughts, ideas, and experiences and, I hope, have challenged and stimulated the profession to address this perennial problem.

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**Institutionalizing Madness: Families, Therapy, and Society,** *by Joel Elizur and Salvador Minuchin. New York, Basic Books, 1989, 251 pp., $24.95.*

The core concern of this book, the dehumanizing force of the mental health system, is indicated in the authors' title *Institutionalizing Madness.* They have chosen consultation to family therapy cases and subsequent follow-up as the path for pursuit of this issue. They conducted a 5-week family therapy seminar and then over the subsequent 5 years followed up the outcome of four families. Through these four families, the authors illustrate their thesis. Their stories draw us into the families, their living circumstances, and their social setting, which includes the special circumstances of kibbutzim in Israel and more ordinary private community settings such as private mental hospitals.

The first story, that of Yoav, is a sad failure. From an attempt at family therapy based on Haley's "leaving home" treatment (1), through increasing institutionalizations, Yoav finally receives a neurological rescue. "Blaming the family" is an important element in this story, and the authors conclude, "Therapy that focuses on the family in isolation is in danger of serving an ideology that values families but resists taking political measures to deal with social factors that overtax them" (p. 62).

The second story is that of Dan, an institutionalized patient in an Israeli hospital. In this story we follow the "consultant" through a series of interventions and/or consultations over 5 years. In this story the therapeutic tactics are revealed as beyond the "structural" Minuchin model. Minuchin uses a variety of other tactics in pursuing his work with this family. This story will be useful for students of family therapy who are developing their own ways and wonder about who to become, and why, in today's mixed up and rich family therapy field.

Joey and Mikey, the subjects of the third and fourth stories, are kibbutzim residents for whom family, school, and community are the important constituent elements. The unfamiliar elements of kibbutz life highlight issues that are similar to the issues faced in our own U.S. society.

In a separate chapter, "Community Management of Mental Illness: An Alternative to Hospitalization," Dr. Mordecai Kaffman includes cases that illustrate his preference for community care rather than inpatient treatment. He makes his points clearly and strongly.

Early in this book Elizur and Minuchin remind us of Jackson's dramatic statement about the "death of the individual" (2). They also include Lyman Wynne's cautionary note about "the individual as subsystem" and remind us that Wynne warned us "not to throw the baby out with the bath water" (p. 63). The authors write compelling stories of their cases, but they might have listened a bit more attentively to Wynne (3) and others. The internal lives of these interesting people remain shadowy at best and are certainly drawn with less intensity than their familial difficulties. Yet Minuchin tells us of his increased sensitivity to individuals due to his father's death in the past and the recent death of his mother. These not only are family events but, as we well know, have profound internal resonations in the individual.

This book, even with these warnings in the middle, remains steadfast in its focus on the outcome of the consultation process and the larger societal context. Certainly family therapy consultants should read this book and wonder about their consultative processes. Yet larger questions are raised for the general practitioner in psychiatry. The deployment of diminishing human services is of increasing concern for all of us. This book raises serious questions about the use of services in the inpatient system as well fragmented resource utilization of outpatient services. It is recommended for the general psychiatric reader as a way of asking unanswered questions about how our field continues to function, relying on hospitalization and fragmentation for some answers and "blaming parents" for others.

The consultative process is often used to provide "answers." This book raises more questions than answers.

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**Homeless in America,** *by Carol L.M. Caton, Ph.D. New York, Oxford University Press, 1990, 222 pp., $29.95.*

**Out of Bedlam: The Truth About Deinstitutionalization,** *by Ann Braden Johnson, Ph.D. New York, Basic Books, 1990, 296 pp., $22.95.*

**Madness in the Streets: How Psychiatry Abandoned the Mentally Ill,** *by Rael Jean Isaac and Virginia C. Armat. New York, Free Press (Macmillan), 1990, 414 pp., $24.95.*

The major public psychiatric development of the second half of this century has been deinstitutionalization. Deinstitutionalization has two facets, an "emptying" of public psychiatric hospitals of patients and a decreased use of such hospitals as a resource for those who become severely psychiatrically ill. In 1955, there were 559,000 public psychiatric beds. Today there are about 110,000. Factors that are credited or blamed for deinstitutionalization include the following.

1. Public psychiatric hospitals began to have an awful reputation in the later part of the nineteenth century; this reached a peak of notoriety after World War II.
2. In the 1950s the concept developed that institutions themselves caused psychopathology beyond that of the original psychiatric illness.
3. Antipsychotic and antidepressive medications were developed in the 1950s. Of course, these medications have been miraculous in altering the lives of millions, but reliance on these medications alone has become a form of abandonment for patients who need far more services to survive adequately in the community.
4. There was a false notion that communities would readily accept the psychiatrically ill.
5. Government agencies had a decreased sense of responsibility for the psychiatrically ill. From the middle of the nineteenth century until the 1960s, each state had a single agency that was fully responsible for the mentally ill. Federal initiatives changed this in the 1960s, and responsibility was fragmented among federal, state, county, city, and "local control" by the 1970s. Moreover, within each of these governments, further fragmentation developed through a multiplicity of agencies (welfare, vocational rehabilitation, housing, public health clinics, psychiatric clinics) that were responsible for specific services for a given patient. This twofold fragmentation, especially given each public agency's tendency to narrowly define its area of accountability, meant that no public agent was exclusively responsible for the psychiatrically ill.
6. Increased use of the private sector contributed to less use of public institutions. The number of private beds in the United States increased from 36,689 in 1970 to 86,009 in 1986, and there was a vast increase in the number of psychiatrically ill patients who began their treatment in the private sector. Although this was a positive development for the vast majority of the mentally ill, the failure of the private sector to be able to provide for comprehensive long-term care and treatment left some "on the streets."
7. Standards set by the Joint Commission for the Accreditation of Healthcare Organizations and by Medicare contributed to deinstitutionalization in two ways. First, it was easier to meet the standards if an institution had fewer patients to treat. Second, the standards call for patient treatment teams to plan for the patient's discharge on admission.
8. An antipsychiatry mood was launched in the early 1960s with a number of writings (by Szasz, Laing, and Kesey) that questioned the values and motives of psychiatry.
9. Increased legal barriers to treatment came in several forms: the "least restrictive" requirement for the care and treatment of the psychiatrically ill in the 1960s, replacing the need-for-treatment standard for commitment with the dangerousness standard for commitment in the 1960s, time-limited commitments in the 1960s, and the right to refuse treatment in the late 1970s.
10. Right-to-treatment judicial decisions, ironically, were met by serving fewer patients so that the imposed standards could be met.
11. Federal entitlements (551, Medicare, Medicaid, Section 8 housing) enhanced the quality of life for numerous patients, but in addressing only part of a patient's need contributed to the abandonment of total care for some. Furthermore, in the 1980s there were reductions in these programs that further increased the number of abandoned psychiatrically ill individuals.

In summary, a massive and untested public policy was launched in the 1960s, made possible by tested medications. Although there have been thousands and thousands of satisfactory placements of patients in the community and thousands of patients have been successfully treated in clinics and offices, no one is claiming deinstitutionalization is a success story. Part of the problem is simply the word "deinstitutionalization." Severely ill psychiatric patients often need lots of services, and they are poorly served by a negative term that sets the goal in terms of what they do not need. Where shall we place the blame for those mentally ill deinstitutionalized patients who are on the streets? Each of these books has a different answer.

Caton's *Homeless in America* is a concise, clear summary of homelessness in the United States, and she underscores Wyatt and DeRenzo's point that public policies, procedures, and programs should receive the same scientific scrutiny that medications receive (1). Her review of the scientific studies of programs, however, finds slim pickings.

Johnson's *Out of Bedlam,* based on considerable personal clinical experience, highlights inept and malefic government agencies and professionals. She writes that deinstitutionalization was not planned and that it has not saved the taxpayers money. A basic mistake, in her experience, was in thinking that to initiate the process was to complete it. Her solution? She advises that there must be a healing of the split between administrators and practitioners, but her description of both is so negative that it is difficult to believe she really has any hope for change.

Isaac and Armat's *Madness in the Streets* is a scholarly and lively review that goes beyond the need for tested programs and beyond the need for responsive bureaucracies and professions. They make the convincing case that good programs, well-functioning government agencies, and responsible clinicians cannot achieve satisfactory care and treatment of the psychiatrically ill within an antipsychiatry culture. They point out that there is a need for a change in public attitudes from antipsychiatry to a new truth: "that mental illness is a tragic reality requiring protective social intervention" (p. 336). There is a need for another Dorothea Dix.

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## PSYCHOANALYSIS

**Freud, Dora, and Vienna 1900,** *by Hannah S. Decker. New York, Free Press, 1991, 284 pp., $22.95.*

This book, by an associate professor of history at the University of Houston, is clearly written and reads relatively easily. It will appeal primarily to those interested in the history of psychoanalysis, and it has a basically polemical thesis. The author attempts to hook up the case of Dora with the political events and prevailing anti-Semitism in Viennese culture in 1900. I did not find her thesis convincing. She writes, " 'Dora' is used in the classroom to assess society's attitude's toward women and the roles it sanctions for them, to study the commingling of familiar pathology and broad-scale malaise, and to illustrate how a psychological illness simultaneously reflects social imperatives" (p. 199). There is considerable overgeneralization of the role of social conditions in trying to explain the case of Dora and a questionable attempt to relate the various prejudices and attitudes of the principal characters in Freud's Dora case to the publications of different well-known Viennese authors at the time.

It is apparently no longer the tradition to teach Freud's case histories to psychiatric residents as it once was; in making presentations at several residency training programs throughout the United States I have learned that a number of them do not offer the residents a chance to study these case histories. In my opinion, this is a tremendous loss for any resident who hopes to go on some day to work with patients in psychotherapy. Freud's case histories are a gold mine of information about psychotherapeutic technique presented by one of the great clinicians of all time and in a manner that is unparalleled in literary style.

Elsewhere (1), I have reviewed the case of Dora from the point of view of learning psychotherapy, and I still believe that it is a masterpiece as well as one of the most important writings on the problem of transference and countertransference. Psychotherapists can learn a great deal from this case. It was, of course, a treatment failure, and I have always believed that one can learn more from one's failures in psychotherapy than one's successes (2). It showed enormous integrity and courage on Freud's part to publish this case, and the history of its publication demonstrates what an intrapsychic struggle Freud must have had before he could get himself to make it public. It remained an unpublished manuscript in his drawer for about 4 or 5 years, and the final version has a number of errors and inconsistencies in it.

Decker does not dwell on that aspect of the Dora case, but she presents an excellent description of the case itself and of the general social and cultural milieu in which all of the principal characters developed. She also makes a number of interpretive generalizations about Freud that are of questionable validity; there seems to be a growing tradition among historians and academics in other fields, such as literature, to speculate about Freud's psyche. Arlow (3) has urged us to see the case histories as "milestones on the road to great discoveries made by a genius. They are major historical documents, but they do not represent modern psychoanalytic thought and practice" (p. 21). The reader of Decker's book should certainly keep this in mind.

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**Projective Identification and Psychotherapeutic Technique,** *by Thomas H. Ogden, M.D. New York, Jason Aronson, 1982, 213 pp., $25.00.*

**The Matrix of the Mind: Object Relations and the Psychoanalytic Dialogue,** *by Thomas H. Ogden, M.D. Northvale, N.J., Jason Aronson, 1986, 260 pp., $25.00.*

**The Primitive Edge of Experience,** *by Thomas H. Ogden, M.D. Northvale, N.J., Jason Aronson, 1989, 235 pp., $25.00.*

This trilogy, the objective of which is to demonstrate the relevance of British object relations theory to contemporary psychoanalysis, has received far less attention than it deserves. In alignment with the goals of psychoanalysis, Ogden aims to repair the effects of disrupted history. "We take for granted that one cannot understand Melanie Klein without understanding Freud," Ogden notes, but he believes that "it is also true that we cannot understand Freud without understanding Klein." A radical notion, especially since Klein has been all but ignored in the United States, but the reader of these three volumes will be hard put to disagree, even though for most of us it is unfamiliar and difficult terrain.

Klein was committed to Freud's drive theory and even held firm to the concept of the death instinct, but she brought an interpersonal frame of reference to psychoanalysis, the want of which has been a major constriction of classical psychoanalysis. There has been a recent proliferation of interest in Klein and the analysts who took her work as their point of reference and departure—Winnicott, Bion, Fairbairn, and others. Ogden summarizes, represents, and creatively extends this body of work.

There is a developmental unity to Ogden's trilogy. *Projective Identification and Psychotherapeutic Technique* describes the window through which object relations theory is linked to clinical data, which informs and is illuminated by it. In *The Matrix of the Mind* he secures the theoretical underpinning of modern object relations theory by reviewing and explicating, especially, the ideas of Klein and Winnicott. In *The Primitive Edge of Experience* Ogden adds to Klein's ideas by introducing a primitive sensory stage into the theory of early development. Throughout all of the books, he illustrates object relations theory clinically and uses it to amplify and revise classical theory.

Projective identification is that process by which one rids oneself of an unwanted mental content, like hate or a feeling of worthlessness, by projecting it into another person and then exerting powerful interactional pressure on the recipient to experience exactly what was projected. In addition to negative contents, the projected part can be something that must be placed externally for safekeeping, like hopefulness in a situation of extreme vulnerability. The therapist who is able to accept the projection and to process it in a manner differently than the patient makes the modified version available for reinternalization. Thus defined, projective identification has four components: it is a defense, a form of communication, a manner of relatedness, and, finally, a pathway for psychological change. Every occasion of transference and countertransference partakes of projective identification in some degree.

The idea that there is something therapeutic about the therapist's containment of the patient's projective identification is based on an interpersonal notion of individual psychological growth. In the range of treatment techniques these interactions richly supplement interpretation without replacing it.

An analyst became aware of feeling guilty toward his patient and recognized that he had become the repository for the patient's disowned and projected belief that he was greedy. The patient repudiated his wish to meet more frequently by devaluing the therapy and making the analyst feel he wasn't worth his fee. Thus informed, the analyst was able to "hold" feelings of appropriate self-interest, derivatives of greed, without being damaged or defensive. He didn't hide that he was glad to be paid for his work, and this made available to the patient a model of processed, detoxified self-interest on which he could begin to examine, modify, and accept those of his own needs which he experienced as greed.

In the final chapters of *Projective Identification and Psychotherapeutic Technique* Ogden theorizes about schizophrenia and arrives at the view that the central conflict in this disorder is whether to allow meanings to exist. In outlining the course of one patient's recovery he shows projective identification articulating the movement from a phase of nonexperience, in which the patient was mute, to a stage of psychotic aliveness that marked his progress into the world and on his way to a fragile form of object relatedness. During a crucial phase the therapist was able to tolerate feelings of estrangement and meaninglessness.

In *The Matrix of the Mind* Ogden speaks of different theories as different languages, each with its unique and contrasting meaning that invites new and enriched syntheses. He strongly argues the case for dialogue between theoreticians of different persuasions. Kleinian theory postulates very early fantasy activity dealing with primitive life and death forces in which the infant must separate the endangered from the endangering. This crucial task is accomplished principally by splitting. Thus, Klein believed the infant capable of well-formed mental activity in the earliest months of life, and this implausible chronology, taken literally, was the agency through which her work was dismissed. Ogden recontextualizes Klein's concepts as organizing structures, like Chomsky's linguistic deep structures—inherent readiness for highly complex and specific developments. Aside from the issue of developmental timing, Klein's two stages of early mental organization have enormous utility in clarifying the nature, development, and transition of schizoid to normal-neurotic stages. This is especially so because Klein traces relational issues in development that expand the purely intrapsychic (oral, anal, and phallic) lines of classical Freudian theory.

Klein described two stages of mental development: the paranoid-schizoid state and the depressive position. In the paranoid-schizoid state there is no central organized agency of self and the infant manages the threat of destructive fantasies by splitting off the loving and pleasureful "me" from the hateful and pain-experiencing "not-me." A primitive order reigns by maintaining discontinuities, and when this defense fails the infant suffers the experience of annihilation. Passage into the second of Klein's developmental phases is marked by an advance across the entire spectrum of mental life: enhanced capacities for differentiation, the use of symbols, modulation of affect, reality testing, and memory. It is the birth of subjective wholeness, concern for others, and the possibility of loss, thus the name "depressive position." Passage into the depressive position does not eliminate paranoid-schizoid issues, however, and a dialectical relationship continues between the two forever in which each state creates, negates, and preserves the other, permeating all future development.

In Ogden's synthesis an object relation necessarily involves a dual subdivision of the ego—a split into two new dynamic suborganizations, each with the capacity to generate meaning and experience. One part is identified with the self in the relationship and the other with the object. The beaten child might have one suborganization that is the cringing helpless child and another that is the sadistic tormenter. Each internal object relation is shaped by some specific relationship but by no means bears a one-to-one concordance with it. The internal object is an idiosyncratic construct derived from interactional reality and the experience of that reality tempered by private fantasies.

Transferences and countertransferences are always enactments of internal object relations, and they are always reinforced by projective identification. Ogden believes that it is necessary for therapists to allow themselves to experience the internal object relations of the patient in order to be able to influence the patient, a point reinforced by Winnicott's theory of the maternal holding environment. In the light of object relations theory, resistance is the difficulty a patient has in relinquishing attachments based on unconscious internal objects. Thus, object relations theory explains the commonplace that a masochistic patient who is improving so often generates a heightened sadism against the self in an attempt to restore the previous balance.

Reflections on the work of Donald Winnicott occupy the final chapters. According to Winnicott, the infant's psychological contents exist initially only within the matrix provided by the mother—a mother-infant unity. A crucial stage of development is the capacity to be alone, which follows from the child's illusion of the mother's presence during her absence and of her absence during her presence. Winnicott sees the issues of separateness very differently than do Jacobson and Mahler because Winnicott's views are rooted in interaction. In order for the externality of the mother to be discovered the child must be sufficiently secure that he can renounce her, let her go, and have her not disappear. The mother must continually provide the physical and emotional presence necessary to survive the infant's fantasied acts of destroying her.

Winnicott's concept of potential space underlies all play, imagination, dreams, and psychoanalysis. It hinges on a dialectic between fantasy and reality. The capacity for transference involves the generation of an illusion that is simultaneously real and not real, and in this "space" meanings can be created, considered, and understood. If the transference experience becomes too powerful it collapses in the direction of fantasy, resulting in a delusional transference. In defense, reality can be exalted through the excessive use of intellectualization and concrete thinking in order to foreclose dangerous imagination.

*The Primitive Edge of Experience* opens with a review of the two Kleinian modes of experience prefatory to the proposal of a third mode: the autistic-contiguous sensory "floor" of experience. "Autistic" refers to the primitive, sensory-organized, isolated self. "Contiguous" refers to the experience of surfaces touching. Once again, Ogden frames a dialectic, here between the isolated interior self and its surface, which touches other people and things. This contrasts sharply with Mahler's phase of "normal autism," which is a "monadic self-sufficient system closed into hallucinatory wish fulfillment." In Ogden's autistic-contiguous mode, objects are experienced in terms of sensory surfaces and interactions with the outside. The normal elaboration of autistic-contiguous organization makes the awareness of separateness bearable. But when the mother-infant dyad is pathologically disordered, the result in the infant is an agony of unboundedness, evoking sensations like leaking, sinking, disappearing, and falling into space.

A regressed patient's refusal to bathe was traced to dependence on his odor. Fear of showering was the terror of dissolving and literally going down the drain. Odor was the vehicle of being something and therefore existing. Ogden uses the autistic-contiguous concept to clarify aspects of the schizoid condition, where the inner world is occupied by persecutors and victims, projections of strangulated object relations cloaked in contempt and grandiosity. Ogden shows how frequently symptoms associated with schizoid conditions devolve upon repetitious sensations of smell, sound, shape, texture, and rhythm—the autistic-contiguous defenses against unboundedness.

In the final portion of this book Ogden thoughtfully plays with the ideas in the space that he has so elegantly developed in these writings. He reformulates the dynamics of entrance into the Oedipus complex, yielding clear and fresh insights; next he addresses "a collection of thoughts . . . to myself (and other novices) on the subject of the opening of the analytic drama" (the first interview); and finally he connects the fear of not knowing to the enduring effects of premature disruption of the mother-infant unity.

The central theme in Ogden's work is the issue of the dialectic. Since nothing ends and nothing passes away, all change takes place in the endless contrast of old and new mental issues that negate and affirm each other to create new levels of complexity and synthesis. "Mental contents exist in a psychological space that is at first almost entirely interpersonal, only later evolving into a personal internal environment. It is the dialectical interplay of our mental contents and the personal and interpersonal psychological space in which they are lived that constitutes the matrix of the mind."

It was a privilege to review these volumes, for they had an immediate effect on my understanding of clinical material, and it is a pleasure to recommend them to every psychodynamic clinician. It is much to be hoped that Ogden's call for dialogue between the various psychoanalytic schools becomes a dream realized. He has contributed substantively toward that end.

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**Encountering Freud: The Politics and Histories of Psychoanalysis,** *by Paul Roazen. New Brunswick, N.J., Transaction, 1990, 337 pp., $34.95.*

On completing his training in political science some 20 years ago, Paul Roazen decided to devote his career to the impact of Freud and his followers not only on politics but on the cultural and intellectual life of this century. He felt that the time had come for an objective and scholarly approach to Freud to correct the largely idolatrous (i.e., Ernest Jones) or hostile attitudes that previously had prevailed in the Freud literature. Roazen has had to traverse a rather rocky road in his endeavor. Ranged against him have been not only the somewhat bemused questionings of his colleagues but, more importantly, the opposition of the Freud establishment and the obstacles placed in the path of any nonanointed Freud researcher by the keepers of the Freud Archive and those, including the Freud family, interested more in protection than scholarship. The lack of recognition of his efforts seems to have generated some feelings of resentment in Roazen, which are evident in at least the early portions of the book under review. Thus, one can wonder whether some of his comments about Anna Freud are influenced by her judgment of him as "a rather malicious American author."

Roazen has persisted, and he has produced a creditable and interesting body of work about Freud and his influence. This includes several books, but much of his critique has been in the form of book reviews—he clearly is an omnivorous devourer and analyzer of works in his chosen and related fields—and this brings us to the current volume. *Encountering Freud* is a collection of essays devoted to different aspects of the Freudian world, largely based on reviews of books about eminent figures in the historical, literary, and political spheres as well as the psychoanalytic sphere. The number of books considered is formidable—I lost count at more than 100—and their catholicity impressive. They range—and this is just a sampling—from Adler and Rank, to Sullivan and Erikson, to Walter Lippman and Hannah Arendt, to Dostoevsky and Orwell (the discussion of the resemblances and differences between Freud and Orwell is illuminating), to Szasz and Bettelheim.

However, employing a series of book reviews as an armature for a general discussion does not produce an entirely satisfactory result. It is responsible for a certain disconcerting jumpiness and lack of cohesion. Some of the subjects considered (the insanity plea, for example) are far afield from the author's main thrust. The books dealt with were published in a period extending from the 1930s to the 1980s, and there are signs that a good deal of the material has been recycled from previous reviews. Some of the comments are now out of date. Thus, in discussing a book by Grier and Cobbs, Roazen uses "Negroes" instead of "blacks," and at another point he states that it would be unacceptable for an analyst to deal with a patient's homosexuality without trying to change it—certainly no longer true. Roazen can also be accused of some carelessness and self-indulgence, evidenced by a considerable amount of repetitiveness and by including very similar reviews of the same book about Walter Lippman in two different chapters. Roazen also assumes a degree of familiarity in his readers about the arcana of psychoanalysis and its disputes that may not be justified. This is particularly apparent in the polemical debate with K. Eissler about whether Freud should bear some responsibility for the suicide of Victor Tausk. This tempest in the psychoanalytic teapot hardly seems to justify the heat generated by it.

These strictures notwithstanding, *Encountering Freud* contains a good deal of thought-provoking material that will be stimulating to psychoanalysts, psychiatrists, academics of different persuasions, and the informed public. I believe that on the whole Roazen has been able to maintain the difficult position of participant observer of the field of applied psychoanalysis. His respect for the master's monumental achievement is evident, but, at the same time, he demythologizes Freud.

So many different subjects are treated in this somewhat overstuffed pudding of a book that an adequate summary of its main themes is not possible. One of these emphasizes the contention, certainly not a new one, that Freud's absolute domination of his followers and his intolerance of dissenters like Adler and Jung and Fromm turned these dissents, which might have been fructifying, into heresies. Roazen sees Freud and his early followers as more gifted, creative, and nonconformist than the later, prosperous members of the Freud establishment. He feels that the absence of some consensus on what constitutes normality in our society has been responsible for accusations, particularly from the political left, that the goal of psychoanalysis is a kind of success-oriented conformity, leading to strengthening of the status quo. He would like to see much more mutual respect and interaction between psychoanalysis and the social sciences and history, with the emphasis being shifted from what psychoanalysis can offer these fields to its reciprocal—what they can offer psychoanalysis.

Finally, this lively book left me with questions about the future of the immense influence exerted by Freud and Freudianism over our entire culture, which, with qualifications, Roazen celebrates. At a clinical level, questions about the therapeutic efficacy of formal psychoanalysis and the economic base underlying its practice are widespread. Although its most enduring legacy to our times, the notion of psychological factors out of awareness affecting our behavior, is secure, many other, more particular elements of Freudian theory are under challenge. The most recent evidence of this critical trend is the disillusionment expressed by Robert Holt (1) in his summing up of 30 years of attempting to rationalize both metapsychological and clinical Freudian theory. To what extent will future biographers, historians, literary critics, and political theorists continue to rely on Freudian insights as the open Sesame to understanding the mysteries of their subjects?

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**New Perspectives on Narcissism,** *edited by Eric M. Plakun, M.D. Washington D.C., American Psychiatric Press, 1990, 252 pp., $28.50.*

This book consists of a collection of articles ranging from a history of psychoanalytic conceptualizations of narcissism, through epidemiologic and empirical statistical studies, and ending with four case presentations by the editor subsequently discussed by Otto Kernberg and Paul Ornstein according to their respective points of view. The stated purpose of the book is "bridging the gulf between psychoanalytic conceptualizations and empirical psychiatry, with those interested in each subject finding something of value, but also an opportunity to learn something from the other's point of view" (p. xiv). All of the six articles in the book are written by professionals who are respectable within their chosen disciplines.

Such a book requires an astute editor with a careful eye on the needs of whoever is to be its intended audience. The assumption must be that the expert epidemiologist will not be sophisticated about psychoanalytic conceptions, the psychoanalyst will not know much about empirical research and statistics, the psychiatrist may not be an expert in any of these areas, and the resident or mental health trainee will need special explanations or attention. At the very least, therefore, such a book should have an index and a summary in simple language of the chapter's main points at the end of each chapter. This book has neither of these vital features. The brief orienting statement by the editor before each chapter does not suffice. In addition, it would have helped to put all the references in one place at the end of the book instead of after each chapter, in order to make them easier to find. Most important, each of the four case histories should have been immediately followed by Kernberg's and then Ornstein's discussions rather than presenting all the cases in one chapter and having Kernberg and then Ornstein both go over all four in their subsequent chapters. The present organization forces the reader to thumb back and forth over and over to follow the discussants against the case histories and to compare them with each other. The title of the book, *New Perspectives on Narcissism,* is misleading because it presents nothing new, only a review of relatively recent concepts and selected points of view. As such, the primary audience should be those who wish to keep up with certain developments over the past decade or two, but not readers who are looking for new ideas or discoveries.

Plakun tells us that his book is to be a "compendium of the leading psychoanalytic conceptualizations of narcissistic personality disorder, with special emphasis on its relationship to borderline personality disorder" (p. xiv), but those who are interested in such psychoanalytic perspectives would do better to read the outstanding work by Abend et al. (1), noting especially their discussion of narcissism on pages 180–184. The opening chapter in the book under review, by James Sackstededer, M.D. (who is not identified as a psychoanalyst), is overly ambitious and tries to include not only psychoanalytic conceptualizations of narcissism but summaries of entire bodies of psychoanalytic theory, which makes for very difficult reading indeed. The editor should have suggested to Dr. Sackstededer that he not include long complex quotations from difficult writers such as Edith Jacobson in the few pages devoted to each theorist. Rather, he could have paraphrased their work in language that less sophisticated readers could understand and confined his review more strictly to concepts of narcissism. There is nothing seriously flawed in what he says, but the style and organization should have been corrected.

The next two chapters, involving epidemiologic data and empirical research data, are reports of preliminary research on small and select groups, and only someone sophisticated in psychiatric research could appreciate and evaluate them.

The last 100 pages comprise the final three chapters presenting the four cases and then discussions of the cases by Kernberg and Ornstein. I was puzzled to find Kernberg's view labeled an "ego psychology–object-relations perspective," which would perhaps mislead the unsophisticated reader into thinking that Kernberg's views are the same as those of Heinze Hartmann's school; they are not. No representative of current traditional ego psychology and psychoanalysis is included in the book, nor is the recent work by Rothstein (2) or the continuing contributions by Masterson and many others. Kernberg is refreshingly honest when he states that the data supplied in the case presentations "preclude anything except speculations" (p. 202). Ornstein more gently recognizes the same limitations but fleshes out his chapter with some review of self psychology.

So, although there is little to oppose in the actual content of the book, I cannot imagine what reader would be willing to plow through it or even be qualified to do so. Psychiatrists interested in Kernberg's point of view or in Ornstein's approach might enjoy their respective chapters, but these authors have developed their theories and approaches at length and using much better case material in many other publications.

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**The Psychoanalytic Core: Essays in Honor of Leo Rangell, M.D.,** *edited by Harold P. Blum, M.D., Edward M. Weinshel, M.D., and F. Robert Rodman, M.D. Madison, Conn., International Universities Press, 1989, 519 pp., $60.00.*

This Festschrift, honoring the many contributions of Leo Rangell, M.D., over a professional lifetime of exciting and consistent high-quality teaching, writing, thinking, treating, and administrative activities, celebrates his 75th birthday. His close friends and colleagues have contributed 25 chapters to this collection of essays. The authors address several topics that relate to their own current work as well as to the earlier contributions of Leo Rangell. Although Rangell's research has focused on the more classic psychoanalytic theoretical and technical approaches, he has, as Blum notes in his dedicatory essay, "also enlarged our vision of group process, political process, and social regulation" (p. 1). In the last chapter of this volume there is a listing of Rangell's publications arranged chronologically from 1942 to the present. In reading these one can follow his development from neurological studies to psychoanalytic contributions.

Rangell has devoted many years to psychoanalytic administrative activities. He was President of the American Psychoanalytic Association twice, President of the International Psycho-Analytical Association twice, and served as President of the Los Angeles Psychoanalytic Society for three terms. Blum's introduction yields biographical data on Rangell's life, accomplishments, awards, and prizes. Arlow's brief personal memoir of Rangell and Rodman's elaboration of the theoretical and clinical contributions of Rangell complete this introductory section.

In the following chapters we find a diversity of topics addressed by leaders in psychoanalysis, such as Weinshel on inconsolability, Brenner on dreams and symptoms, Harley on the primal scene, and Wallerstein on psychoanalysis and psychotherapy. It is not space effective to list all of the other authors and their very stimulating topics. These contributions include essays by colleagues from England, France, Israel, Spain, Holland, and the United States. Many of the authors are basically oriented to ego psychology. The papers themselves are clear, well written, clinical, and theoretical, and they give the reader an excellent overview of current psychoanalytic contributions. There are papers, for example, on developmental psychoanalysis, ethics, psychoanalytic organizations, and holocaust studies.

This is a fitting tribute to a devoted, hard-working, pioneering psychoanalytic teacher. I am certain that he is proud and pleased by the tribute paid him by his friends and esteemed colleagues. For those of us who wish to see what some of our leading colleagues are working on, this volume, although not saying it all, says so much that it can and should be read by psychoanalysts the world over. The editors are to be congratulated for bringing us closer to one of the pivotal current psychoanalytic cores.

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## FORENSIC PSYCHIATRY

**American Psychiatric Press Review of Clinical Psychiatry and the Law, vol. 1,** *edited by Robert I. Simon, M.D. Washington, D.C., American Psychiatric Press, 1989, 373 pp., $38.50.*

In the preface to this volume, the editor recalls that capable psychiatrists at a hospital where he attended grand rounds panicked after being sued for the first time. Some of the attending staff "darkly hinted at early retirement." With the well-known increase in psychiatric malpractice litigation in recent years, fear and defensive psychiatry have begun to jeopardize self-confidence and sound clinical practice. The increase in litigation is paralleled by greater legislative and judicial regulation of the profession. Ethical guidelines promulgated by APA and other professional organizations interface with legislative statutes and judicial decisions in complex and sometimes conflicting ways. In this atmosphere of anxiety and confusion, the clinician would do well to learn more about his or her ethical and legal responsibilities. The reviews in this volume are a good place to start. The authors are experienced clinicians who provide practical advice on how to avoid legal entanglements, but, more importantly, they keep in mind the broader question of how to do so while promoting the best possible patient care. They educate about clinical practice while informing about the law.

Volume 1 is divided into four sections, each with its own editor, covering Somatic Therapies and the Law, Confidentiality in Psychiatric Clinical Practice, The Duty to Warn, and Psychiatric Legal Diagnostic Dilemmas. Three feature articles follow, in which recent legal decisions are summarized, a hypothetical case of negligent care of a suicidal patient is presented with arguments from both sides, and instructions are given on how psychiatrists should conduct themselves in the courtroom. The hypothetical case and arguments that follow are particularly well written and elucidate many of the ethical and legal dilemmas discussed in the rest of the book. However, a case directly related to the topics of the previous sections would have been more suitable.

In his section on somatic therapies, Simon adheres firmly to the idea that the best way to avoid lawsuits is to practice good clinical care with a knowledge of the law at hand. He clearly maps out areas of pretreatment and posttreatment liability, advising us to protect ourselves through adequate assessment of the patient, proper attention to diagnosis, informed consent, record keeping, and careful ongoing risk/benefit analysis. The all-important issue of standard of care is well covered, with cases to illustrate court rulings on this matter. In most instances, psychiatrists are free to exercise their best clinical judgment, as long as they have professional guidelines, accepted practice, or clinical studies to back them up. Defensive psychiatry can be bad psychiatry and so make us more vulnerable to lawsuits. This section contains a good discussion of treatment dilemmas posed by tardive dyskinesia, with practical guidelines for avoiding liability. Overall, Dr. Simon does a good job of guiding us between the Scylla and Charybdis of careless treatment and unwarranted defensiveness.

Confidentiality and privilege are areas in which the legislature and courts have become increasingly more involved. The authors of this section review the historical, ethical, and legal aspects of these concepts and the limits of both with an eye toward identifying areas of competing duties. Should one release information to an employer or insurance company that may be damaging to the patient and ultimately compromise the therapeutic alliance? Here the economic realities of modern society, readily apparent to the courts, may infringe on less comprehensible processes that take place in the privacy of the office. The authors do not dodge these issues but attempt to identify them, to clarify the ethical and legal dilemmas involved, and to call for changes when they recognize conflicts between patient care and unreasonable legal requirements.

They provide assistance in charting the best course through difficult decisions, again with optimal patient care foremost in mind. Issues of confidentiality in the era of AIDS, in disputes over child custody and visitation, and with children and adolescents are covered in separate chapters with plentiful reference to legislative statutes, case law, and ethical codes.

The topic of the duty to warn logically follows confidentiality because these are two potentially conflicting duties the clinician may face in practice. The five chapters in this section range in coverage from the moral and political underpinnings of the duty to warn (more properly the duty to protect) through practical issues of how to manage potentially violent patients, including those behind the wheel of a car. Drs. John W. Douard and William J. Winslade argue that the conflict between confidentiality and the duty to protect is rooted in the moral imperative to protect those who are vulnerable and dependent. This includes third parties as well as the patient. Both are entitled to equal concern and respect derived from the right to equality. Problems arise when the courts, in the absence of legislation, must decide to what extent third parties include those not specifically named by the patient. Are we as therapists responsible for protecting all of society at large? The trend has been to increase our responsibility to third parties while concurrently protecting the civil rights of the patient with regard to involuntary commitment. This results in the clinician's increased vulnerability because more weight is placed on the proper exercise of due care. The situation is exacerbated by the fact that the extent of the clinician's duty to protect is often unlegislated and, therefore, subject to variable court decisions. Whether or not one agrees with Drs. Douard and Winslade that greater legislative action is needed, it is clear that the clinician is now more vulnerable and needs to weigh conflicting duties carefully.

Dr. James C. Beck, in his chapter on the clinical aspects of the duty to protect, provides valuable insights into the practical aspects of assessing and managing potentially violent patients and handling conflicting duties. The *Tarasoff* principle is really a duty to protect in which warning a third party is only one way of discharging that responsibility. Dr. Beck shows how to preserve the therapeutic alliance by matching alternatives to the level of concern for violence. In the end, a violent patient may be relieved by the clinician's exercise of restraint, even if this means warning a third party or hospitalizing the patient involuntarily. The important thing is how one conducts oneself with the patient. Dr. Beck's discussion, based on his own experience and using clinical examples, is very helpful in reconciling our concern for the patient with our responsibilities to society.

In the last section of these reviews, Dr. Harold M. Ginzburg discusses the concepts of negligence, dangerousness, the duty to protect, and emotional harm from the point of view of the evolution of legal theory and its relation to psychiatric knowledge. Some of the same ground covered in previous reviews is covered here, but in more detail and with greater emphasis on court decisions that have influenced these concepts. Dr. Ginzburg points out that "dangerousness" is not a *DSM-III-R* diagnosis, yet according to the California Supreme Court majority rule on the *Tarasoff* case, therapists in their capacity as professionals are virtually expected to predict dangerousness. Studies have shown that therapists are not able to predict dangerousness with any certainty; therefore, these court decisions are not congruent with our knowledge about what psychiatrists are able to do. Dr. Ginzburg shows how dissenting opinions in California, Colorado, and elsewhere make the duty to protect still a much debated concept. Although aspects of the duty to protect may be at odds with psychiatry, the legal concept of emotional harm has evolved in ways consistent with psychiatric knowledge. We know that psychological trauma can result from experiences other than physical harm, and the courts have reflected this in their decisions about what constitutes emotional harm. This section is interesting for its legal theory but would have been enhanced by greater discussion of psychological concepts and an attempt to find solutions to these psychiatric-legal dilemmas.

This collection of reviews goes far toward introducing the clinician to the interaction between psychiatry and the law. The topics range from fundamental moral issues to very practical problems of patient management. Throughout, the focus is on facilitating good clinical care rather than on just avoiding lawsuits. Although this book abounds with citations of ethical codes, legislative statutes, and case law, readers quickly realize that they must get to know the ethical codes in full and the statutes in their own states. In addition, one must have adequate malpractice insurance, and a more than passing familiarity with a forensic psychiatrist may prove helpful. Readers of this book will be more knowledgeable about conflicts of duty and better prepared to handle them. The waters may be rough, but there is no need to jump ship.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Cognitive Impairment in Dramatic Personality Disorders

SIR: Several recent articles have demonstrated neurocognitive impairment in subjects with borderline and other dramatic personality disorders (1–3) despite long-standing empirical evidence that cognition in persons with personality disorders falls within population norms (4). Several hypotheses attempt to explain why cognitive impairment has not been demonstrated by normative comparisons: 1) past studies may have used the wrong cognitive measures (e.g., failed to use tests of prefrontal functions) (1); 2) the effect can only be demonstrated in selected test populations (e.g., markedly impaired patients or high-performing control subjects); 3) the effect is highly variable and/or not normally distributed across patients and test measures; or 4) the effect is either very slight or spurious.

We tested these hypotheses by administering neurocognitive screening tests to a group of patients with personality disorders. The subjects were 25 male patients, mean±SD age=37.2±5.5 years, in a milieu therapy program at a Veterans Administration hospital. All had diagnoses of mixed personality disorders within the dramatic cluster (*DSM-III-R* cluster B), with borderline and antisocial disorders predominating. The subjects had past histories of substance abuse, but continuing abstinence was confirmed by taking random weekly observed urine samples. Only three individuals had lifetime histories of head trauma sufficiently severe that they had sought medical care. The group was high functioning to the extent that members successfully negotiated cognitively and emotionally demanding milieu rules and activities; many held part-time jobs in the community during the day.

Neurocognitive tests (5) included the Benton Figure Drawing Test (Form 1, Administration C, norm ≥6/8), the Reitan Trails B test (norm ≤99 seconds), the WAIS Digit Symbol test (norm ≥34), the difference between verbal and nonverbal IQs on the Hartford-Shipley test (norm ≤20), and a Luria repetitive figure drawing task (norm ≥6/7). The number of patients with scores below these norms was compared to the expected distributions by means of chi-square tests.

The results showed 32% of the patients scoring below norms on the Trails B test ($\chi^2$=11.77, df=1, p=0.001), 25% with verbal IQ greater than nonverbal IQ by 20 or more points ($\chi^2$=6.32, df=1, p=0.01), and 16% below norms on the Benton test ($\chi^2$=4.76, df=1, p=0.03). Twelve percent of the patients were below norms on the WAIS Digit Symbol test, and 10% were below norms on the Luria repetitive drawing test; these differences were not significant.

These results demonstrate that a high proportion of patients with dramatic personality disorders may show neurocognitive deficits when their test scores are compared with general norms. These neurocognitive tests are sensitive to brain dysfunction across many brain loci, but they are not specific for impairment in any brain area(s) (5). Their ease of administration should enable other researchers to test these findings and/or assess the clinical importance of neurocognitive impairment in their own patients. Patients who show deficits on general cognitive screening tests could then be given a comprehensive workup, which could point to any focal areas of cognitive dysfunction (1).

Our results support hypothesis 3: that cognitive impairment is quite variable across patients and between different test measures. The sources of this variability and its meaning for theories of personality disorders are yet to be determined. Cognitive dysfunction may have implications for both our understanding and our treatment of patients with personality disorders (1–3).

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## Ineffectiveness of Clomipramine for Obsessive-Compulsive Symptoms in a Patient With Schizophrenia

SIR: Although the relation between obsessive-compulsive disorder and schizophrenia has been debated for decades (1), obsessions and compulsions do occur in a considerable number of persons with schizophrenia. Treatment has not helped (1), and outcome has been poor in some series of patients (2). There have been a few reports (3–5) of the use of clomipramine for obsessive-compulsive symptoms in schizophrenia that suggested improvement in a majority of the patients treated. However, some patients became more psychotic. With the recent general availability of clomipramine, this drug will surely be increasingly tried in schizophrenic patients with obsessive-compulsive features. Clinicians should be aware of the potential for some of these patients to worsen when treated with clomipramine. We report such a response in a patient with chronic schizophrenia and marked ritualistic compulsions.

> Mr. A was a 33-year-old man with chronic undifferentiated schizophrenia who had been in the hospital 8 years and had had seven previous hospitalizations in as many years. He exhibited a wide variety of bizarre and persecutory delusions, auditory hallucinations, and aggressiveness controlled but not eliminated by antipsychotic medication. He also showed poor concentration, poor self-care, restless-

ness, intrusiveness, and episodic excessive water drinking, but he was generally friendly and cheerful. In addition, he had repetitive stereotypical behaviors with an evident compulsive quality. For example, he would stand in the hall or day room, repeatedly taking his shoes off and putting them on and lacing them up, with periodic pauses. He would not move until he had finished, even during ward meetings. Similarly, he would put his shirt on and take it off, button and unbutton his pants, and touch walls, doors, and garbage cans in a compulsive manner. When asked why he engaged in these ritualistic behaviors, he generally had no explanation. These symptoms had not responded at all to treatment with numerous antipsychotics including clozapine. There was no sign of organicity on mental status, neurological, and CT scan examinations.

Mr. A had previously shown no response and some increased agitation, hostility, insomnia, and paranoid ideation when taking fluoxetine, 60 mg/day, added to thiothixene. A regimen of clomipramine, 25 mg/day, was started and slowly increased over 10 weeks to 250 mg/day, while he continued to take mesoridazine, 300 mg/day. No change in his compulsions was observed during this time, but between weeks 2 and 6 he was reported to be more hostile, paranoid, and angry. The dose of mesoridazine was increased to 400 mg/day, and there was temporary improvement. Two weeks after his dose of clomipramine had reached 250 mg/day, he was again suspicious and hostile, abusive, aggressive, and more deluded. The mesoridazine was stopped, and perphenazine was started and increased to 64 mg/day. Two weeks later, clonazepam was added and increased to 6 mg/day, which calmed him and controlled his aggressiveness. He continued to take 250 mg/day of clomipramine for 8 weeks, with no change in his compulsive behavior. After the clomipramine was reduced and stopped, the clonazepam was also reduced and stopped without recurrence of the hostility and aggressiveness.

In this case clomipramine caused a slight worsening of the psychosis and agitation, with no effect on the obsessive-compulsive symptoms. Clomipramine is a relatively selective serotonin reuptake inhibitor and has been found to be helpful in obsessive-compulsive disorder, suggesting a central serotonergic dysfunction in patients with this disorder. The lack of effectiveness of serotonin-enhancing strategies in this patient with schizophrenia and obsessive-compulsive rituals argues against a serotonergic dysfunction mediating his obsessive-compulsive symptoms.

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## Oral Caffeine Augmentation of ECT

Sir: For geriatric major depression, ECT is one of the most effective and safe treatments available. However, the practice of ECT continues to be refined in order to improve further its efficacy and side effect profile.

One area of research is the factors affecting seizure threshold; seizure threshold increases with age and during a course of ECT (1). These factors are important in the treatment of elderly patients. Missed or inadequate seizures may preclude a response in patients for whom ECT is the last viable treatment option. If bilateral ECT is used, acute cognitive side effects may result.

Intravenous caffeine will extend seizure duration during ECT without causing anxiety or affecting hemodynamics associated with ECT (2–4). Intravenous caffeine sodium benzoate is not available in Canada, and there are no published reports on the use of oral caffeine augmentation. We have been prescribing oral caffeine and successfully lengthening seizures that had previously fallen below 25 seconds in duration. For more than 30 depressed geriatric patients, we have used 100-mg caffeine tablets dissolved in 5 ml of water, administered 1 hour before treatment. We titrated the dose (300–1000 mg per treatment) according to response. The higher dose was usually required later in treatment.

Our geriatric patients did not experience any additional complications when caffeine was added to their ECT regimen. We found no evidence of peri-ECT complaints of anxiety or dysphoria and no serious cardiovascular, hemodynamic, or anesthetic complications.

While none of our patients who received the caffeine augmentation displayed abnormally prolonged seizures or dramatic cognitive deficits, there are reports suggesting that post-ECT delirium and memory loss may be associated not only with stimulus intensity but also with seizure duration (5). Therefore, the potential benefits of oral caffeine may be diminished if seizure duration becomes excessive. However, it has been our experience that oral caffeine augmentation will decrease the frequency of missed or inadequate seizures without an increase in adverse effects, thus minimizing the need for higher stimulus dosing and a protracted course of treatment.

Further work needs to be done to determine whether caffeine-augmented ECT would not only convert failed seizures but also allow for successful unilateral ECT in cases in which bilateral treatment had been previously used.

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## Pharmacotherapy and Psychotherapy for Major Depression in a Man With AIDS

SIR: There have been relatively few reports of the treatment of depression coexisting with AIDS (1, 2). We report the success of combined pharmacologic and psychotherapeutic treatment of major depression in a man with AIDS.

> Mr. A, a 38-year-old man in a long-standing homosexual relationship, was admitted to a psychiatric unit with a 6-month history of major depression (nonpsychotic, single episode). Results of cognitive testing, physical examination, RPR, thyroid studies, and EEG were all normal. His symptoms included profound and unremitting dysphoria, passive suicidal ideation, hypersomnia, poor concentration, indecisiveness, and decreased libido, interest, and appetite. His Beck Depression Inventory score was 34, indicating severe depression. Although his illness was stable at admission, he had developed AIDS almost 4 years earlier, with the diagnosis of Pneumocystis carinii pneumonia. Complications included two further bouts of this pneumonia and cytomegalovirus retinitis.
>
> Nortriptyline was started and the dose adjusted to a serum level of about 100 ng/ml. After 2 weeks, Mr. A's depressive symptoms had diminished considerably and he was discharged. He elected to begin weekly psychotherapy, which centered on a "being-with" contact (3) involving an active and supportive approach as a means to bolster appropriate defenses and to broach issues about his illness. Subthreshold depressive symptoms gradually diminished and were absent 3 months after discharge. Mr. A completed a will and resumed contact with estranged relatives. His relationships improved markedly, and he noted profound satisfaction from his social contacts. Concurrently, his medical status worsened: he developed monocular blindness from a vitreous hemorrhage, pulmonary "atypical" tuberculosis, severe fatigue, and pancreatic insufficiency. His Beck depression score 7 months after admission was 13, entirely attributable to physical symptoms. He died of an undiagnosed pneumonia 9 months after admission.
>
> Because Mr. A was followed in the Multicenter AIDS Cohort Study (4), additional data were available. Magnetic resonance imaging scans of his brain 4 months before and 7 months after admission showed marked volume loss. Serial neuropsychiatric testing did not document appreciable cognitive decline.

This patient evidenced an excellent response to pharmacotherapy and supportive psychotherapy despite significant physical deterioration. While some degree of "depression" is expected with a terminal disease (5), his condition deviated from this considerably; rather than being preparatory, his depression markedly interfered with the process of dying. If his case can be generalized to those of others with AIDS, treating major depression can yield substantial benefit.

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## Seizure With Low Doses of Clozapine

SIR: We were interested in reading "Clozapine and Seizures" by Ellen Haller, M.D., and Renée L. Binder, M.D. (1), who proposed useful clinical guidelines for managing the risk of seizure with clozapine treatment, which seems to be higher than with other antipsychotic drugs, according to a dose-dependent relationship.

The authors reported four cases and mentioned two previously published cases (2) of seizures with clozapine. Among six patients, only one received low doses of clozapine (75 mg/day), but that patient had a preexisting seizure disorder. High doses (more than 600 mg/day), rapid dose increases, polypharmacy, and organic pathology were mentioned as risk factors for seizures with clozapine.

We report the case of a patient with none of these risk factors who developed convulsions while taking clozapine.

> Mr. A was a 30-year-old man with a 2-year history of paranoid schizophrenia, which had been resistant to haloperidol, 20 mg/day. Neither seizures nor substance abuse was mentioned in his past history. He was placed on a regimen of clozapine therapy alone, after haloperidol had been stopped for a week. Results of a pretreatment physical examination, laboratory tests, and an EEG were within normal limits. The initial dose of clozapine was 25 mg/day, with a 25-mg increase every 2 days. When receiving 150 mg/day, on the 13th day, Mr. A had a generalized grand mal seizure that was witnessed by ward staff members. An EEG made 2 days after the seizure showed bilateral ictal activity with spikes over basal areas. Clozapine was then immediately stopped, and electrical disturbances slowly lessened in 10 days, as shown by repeated EEGs.
>
> The findings of a CT scan were normal, and other possible causes were eliminated. The patient refused to continue to take clozapine, even with anticonvulsive treatment. He was later given pipotiazine, 60 mg/day, and his EEG remained within normal limits after 8 weeks of treatment, but psychiatric improvement was still minimal.

This report is consistent with the conclusions of Dr. Haller and Dr. Binder, suggesting that clozapine treatment necessitates particular care with respect to seizure risk. Our patient had a convulsion at the very beginning of treatment, with low doses; the dose increase was prudent; he was taking no other drug; and he showed no clinical or EEG ictal activity with either haloperidol or pipotiazine.

In addition to the recommendations of Drs. Haller and Binder, we propose keeping a close watch over EEGs at the beginning of treatment, during increases in dosage, until a maintenance dose is reached. Such supervision may be useful in detecting electrical but subclinical ictal activity, which would imply slow increases in dosage. Further observations will be necessary to determine whether these precautions are valid for avoiding seizures with clozapine.

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### Flunarizine as Maintenance Treatment of a Patient With Bipolar Disorder

SIR: The efficacy of lithium in the long-term treatment of bipolar disorder is well documented (1). However, there are patients who experience severe side effects from lithium. For them we must have an alternative. The efficacy of calcium channel blockers in the treatment of affective disorder has been demonstrated in several studies (2–4). Verapamil has been used in acute manic episodes as well as in maintenance treatment. There are also isolated reports of the use of other calcium antagonists in treating affective disorders, but none involving long-term treatment (3).

We report on a patient with bipolar disorder (*DSM-III-R*) who has been treated for more than 3 years with flunarizine (Sibelium; Janssen Pharmaceutica, Piscataway, N.J.). Flunarizine, a selective calcium-entry blocker, is used for several conditions, including migraine, and the recommended dose is two 5-mg tablets once daily, which is also the dose used by our patient.

Ms. A, 36 years old, has a family history of affective disorder. Since her first attack at the age of 17, she has had more than 20 episodes of affective illness. Since the age of 19 and up to the time when she was given flunarizine, she had been hospitalized 15 times for manic and depressive episodes, mainly for mania. Despite therapeutic plasma levels of lithium, the attacks remained severe and necessitated the use of high doses of neuroleptic agents. She was also given ECT and showed clear improvement. Her long-standing lithium-induced hypothyroidism was treated with L-thyroxine sodium. Severe adverse reactions—diarrhea, acne, and severe tremor—necessitated discontinuation of lithium. She was considered free of detectable organic disease and without contraindications for treatment with flunarizine. Flunarizine was substituted for lithium without a washout period.

The diarrhea ended in a few days, and Ms. A was free from acne within a month. Her mental health improved as the side effects disappeared. She has been working and functioning well. Routine medical checkups, including hematological and biochemical assessments, have been carried out regularly without any abnormal findings. The drug has been well tolerated, and no side effects have been encountered. Steady-state plasma levels have varied between 34 and 91 ng/ml. After nearly 3 years of maintenance treatment with flunarizine, Ms. A developed a moderate depression in connection with a stressful life event. At her own request ECT was used, and she clearly improved. There was no need to discontinue the flunarizine treatment.

Flunarizine may be effective as an alternative to lithium for patients who are unable to tolerate lithium's side effects. The limitations of an isolated case report, however, are obvious, and no firm conclusion can be drawn from it, although the treatment period in this case has been long. The patient has also been euthymic for a longer period of time than when she was taking lithium. It seems likely that the brief depressive attack was brought about by the stressful event rather than being drug-related. However, there is a need for well-designed longitudinal studies to evaluate the potential efficacy of flunarizine as a prophylactic treatment for bipolar disorder. Such a study is planned.

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### Methadone Treatment of Tourette's Disorder

SIR: The following case illustrates the use of methadone in the treatment of Tourette's disorder.

Mr. A, a 43-year-old man, had suffered from various tics since the age of 12, except for 2 months during his 21st year and a few shorter periods afterward. His motor tics consisted of repeated eye blinking, dangerous motions with objects (cigarettes, knives, and the like), sudden jumping up, copropraxia, etc. His vocal tics consisted of coprolalia, echolalia, and palilalia. Moreover, Mr. A suffered from inner tension, obsessive and self-mutilating thoughts, compulsive acts, and sleep disturbances. In recent years, lithium carbonate and lormetazepam had been prescribed because of manic episodes. In 1989 Mr. A was admitted to our psychiatric hospital because of alcohol abuse. His consumption of alcohol had increased after the tics increased. In the past he had been treated with a variety of medications: zuclopenthixol, fluphenazine, thioridazine, haloperidol, pimozide, clonidine, and a combination of sulpiride and verapamil. Akathisia occurred with each drug, and there was only a doubtful effect on the tics. Cannabis, tried once, had no effect on the tics and worsened the inner tension. Alcohol also did not influence the tics, although they were experienced as less irritating.

After a medical staff meeting in which there was discussion of the case of a man suffering from Tourette's disorder whose tics disappeared when he used heroin and, later on, methadone (1), it was decided to try methadone for Mr. A. He promised to stop alcohol abuse, and a contract was made in which both the patient and the therapists had the right to stop the methadone treatment. The treatment started at 30 mg/day of methadone, and the dose was raised in regular increments over 26 weeks to 110 mg/day. Gradually, the tics diminished in number and intensity. Mr. A also succeeded in postponing them during conversation, bus travel, etc. He resumed riding a bicycle and handled sharp objects without difficulties. To evaluate the effect of the drug several times under identical circumstances, we counted tics during five different administrations of the Rivermeet Behavioural Memory Test. The number of tics was reduced to one-quarter, from 72 tics per 20 minutes without methadone to 18 and 19 tics at doses of 90 and 105 mg/day of methadone, respectively. Mr. A's scores on the Hamilton Rating Scale for Depression gradually decreased from 13 without methadone to 2 at a dose of 105 mg/day. When he first started methadone, there were temporary side effects: nausea, itching, and hesitation on micturition. Moderate chronic constipation and some languor in the early morning remained permanently.

After 56 weeks of continuous treatment, Mr. A is still using 110 mg/day of methadone. We cannot establish that he has developed tolerance to the drug. When we again counted tics under the standard circumstances, there were 23 tics in 20 minutes, and again the depression scale score was 2. There is no longer alcohol abuse. Our impression is that methadone treatment is successful in this patient with Tourette's disorder.

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### Situational Influence on Development of Delusions of Pregnancy in a Man

SIR: We read with interest the letter of Georges Bitton, M.D., and associates (1) about delusions of pregnancy in a man. The authors made the point that such delusions have usually been reported in men with organic brain damage but that their case illustrated a similar phenomenon in the absence of identifiable cerebral pathology. We would like to extend their observations further with a case illustrating a strong situational influence on the development of delusions of pregnancy in a man.

Mr. A, a 34-year-old divorced, bisexual man, was admitted to a general psychiatric unit with an episode of mania with psychotic features. His diagnoses were bipolar mood disorder and alcohol abuse. The latter was not prominent at the time of admission and had caused no identifiable permanent cerebral damage. Results of a neurologic examination were within normal limits, and there was no evidence of cognitive impairment on mental status examination. HIV test results were negative.

The psychotic symptoms initially consisted of persecutory delusions quite similar to those the patient had experienced during previous manic episodes. However, the unit to which he had been admitted during this and prior episodes had recently developed a subspecialty program for the care of pregnant mentally ill women. Pregnant women in their third trimester occupied four of the unit's 18 beds and received specialized treatment, including group treatment, nutritional supplementation, and educational programs geared to their needs (2). Mr. A began to spend a great deal of time with these women. He then began to order double meals and drink all of the milk supply for the pregnant women. He gained considerable weight and began wearing large, loose-fitting clothes. When questioned about this behavior, he asserted that he too was pregnant. He would pat his abdomen and say, "I don't feel the baby moving" and "I shouldn't be smoking these cigarettes; they're bad for the baby." He questioned female nursing staff members about how labor had been for them, so that he would know what to expect. He had two daughters whom he had missed greatly since his divorce, and he now spoke of how he would have another one. He wanted very much to join the unit's groups for pregnant patients.

As his mania cleared, the patient recognized these ideas as delusional and spoke in a rational way about wishing he could be a better father to his daughters. Although his longing for his daughters had been a chronic concern, delusions of pregnancy had never appeared before and did not recur in a subsequent episode.

Although the numbers are too small for statistical corroboration, it is the impression of the staff on this unit that since the introduction of a subgroup of visibly pregnant patients who receive special treatment, there has been a notable increase in delusions of pregnancy among other patients who are not pregnant or delusions that a significant other is pregnant. Contextual variables may exert a strong influence on the content of such delusions, particularly in cultures or settings in which pregnancy confers a highly valued social status.

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### Differentiating Paranoia and Legitimate Fears

SIR: I was interested to read about the "paranoid" patient who really was being chased by the Mafia and police (1). That account reminded me of the following case.

Mr. A came to the emergency department of a psychiatric hospital in Canada and requested a supply of thiothixene. He stated that he was a U.S. citizen and had been receiving treatment for schizophrenia in several U.S. hospitals for a number of years. He claimed that some years earlier, while he was watching a news broadcast on television, he had made an idle remark about Presidential assassination. His comment was reported to authorities, he was convicted of threatening the life of the President, and he served a sentence in a federal prison. He received psychiatric care while serving the sentence.

Mr. A claimed that after his release he was followed everywhere by Secret Service agents, and as a result of their harassment he was unable to hold down jobs or find a permanent residence anywhere in the United States. In desperation he had come to Canada, hoping that Canada would provide refuge from the persecution he felt in the United States. He expected to begin a new life here. Although Mr. A exhibited no signs of mental disorder, his statements about receiving treatment for schizophrenia sounded plausible, and his comments about Secret Service agents seemed consistent with that diagnosis. He was given a small supply of thiothixene and an appointment to return in 2 weeks' time.

Six days later Mr. A reappeared in the emergency department. He was very distraught. He claimed that Secret Service men had located him and were following him on the street and that one agent had snapped a picture of him from behind a parked car. He felt that it was pointless to pursue his goals in Canada, and in his disheartened mood he considered drowning himself. He was easily persuaded to be admitted to a hospital, feeling he would be protected from harm and helped to resolve his problems with U.S. government authorities. The admitting diagnosis was acute situational maladjustment associated with paranoid schizophrenia.

Soon after Mr. A's admission, the hospital received a call from a Canadian immigration official. He identified Mr. A by name and inquired whether he was receiving psychiatric care. He indicated that U.S. government agents were interested in Mr. A's whereabouts. After some discussion, Mr. A agreed to meet with Canadian officials to discuss his eligibility for political asylum in this country. He felt optimistic about this turn of events and requested discharge from the hospital. He made no further contact with the hospital after his departure.

The U.S. Secret Service keeps permanent files on individuals who have made threats against the President. These individuals are subject to frequent monitoring and security evaluations by agents within and outside the United States (2). Like Mr. A, many patients who have been identified as potential threats to the President or other White House figures are white, unmarried men suffering from paranoid schizophrenia (3). His account of persecution by undercover government agents, like the tale of persecution by New York Mafiosi and police told by the patient in the case reported by David Mayerhoff, M.D. and associates (1), sounded implausible and pathological. As Dr. Mayerhoff and colleagues reminded us, sometimes "paranoid" people have real persecutors.

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### Relation of Age to Prevalence of Tardive Dyskinesia

SIR: Vikram Khot, M.D., and Richard Jed Wyatt, M.D. (1) reported a meta-analysis of nine studies to provide age-specific estimates of the prevalence of neuroleptic-associated dyskinesia (more than 3 months' exposure to neuroleptics) and spontaneous dyskinesia (less than 3 months' exposure to neuroleptics). Both of these conditions were reported to increase sharply in prevalence from age 16 to 59 years, followed in later years (up to age 89) by a plateau or modest decline in their prevalence rates. Age-specific rates of true tardive dyskinesia were calculated by subtracting age-specific rates of spontaneous dyskinesia from corresponding rates of neuroleptic-associated dyskinesia. The authors found that "the true prevalence of tardive dyskinesia changes relatively little with increasing age."

We rated the presence and severity of dyskinetic movements for 45 elderly patients (mean±SD age=72.4±8.1 years, range=60–91) who were admitted for acute inpatient care to the geriatric clinical research unit at our facility (2). Cases of dyskinesia required a rating on the Abnormal Involuntary Movement Scale of mild in at least two body areas or moderate in at least one body area. Only seven (16%) of the 45 patients exhibited dyskinesia, all of whom had received previous treatment with neuroleptic medications. In the 12 patients without any history of neuroleptic exposure, we detected no cases of dyskinesia.

Although increasing age appears to be associated with greater prevalence of dyskinesia between the second and sixth decades, there is a growing body of evidence that this association does not exist among patients over the age of 60. In addition to the results presented by Dr. Khot and Dr. Wyatt, Smith and Baldessarini (3), in a separate meta-analysis of nine studies, found no significant increase in the prevalence of tardive dyskinesia in patients over age 70 (N=559) compared to those between ages 60 and 70 (N=566). In a prospective study of tardive dyskinesia in the elderly, Saltz et al. (4) reported that "age did not have any significant effect on the prevalence of tardive dyskinesia within the age spectrum of 57 to 96." Similarly, in our study the mean±SD age of the patients who exhibited dyskinesia did not differ significantly from that of the patients without dyskinesia (73.7±8.9 and 72.1±8.0, respectively; t=0.5, df=43, p=0.60). We concur with Drs. Khot and Wyatt that the risks of developing abnormal movements from neuroleptic medications may be less than previously thought, particularly in the elderly. If tardive dyskinesia results from the supersensitivity of striatal dopamine-mediated synapses, the prevalence of this condition may cease to increase after age 65 because of the reductions in striatal neurons and dopamine content that are concomitants of normal aging (5, 6).

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### Control Groups in the Study of Effects of Medication

SIR: In their article "Neuropsychological Performance in Medicated and Unmedicated Patients With Tourette's Disorder," R.A. Bornstein, Ph.D., and Victoria Yang (1) correctly emphasized that medication effects are best elucidated through the study of the same group of patients before and after initiation of treatment, i.e., with patients serving as their own control subjects. Nevertheless, their study of the effects of medication in parallel groups (medicated versus unmedicated) of patients with Tourette's disorder is a methodological advance beyond studies that rely solely on behavioral and cognitive changes elicited by therapeutic agents in normal healthy volunteers.

Implicit in the study of drug effects in normal subjects is the idea that the disorder per se causes no diminution in performance. Decremental performance effects demonstrated in normal subjects are then attributed to drugs required by a population of patients for the treatment of a preexisting disorder. For example, inferences are often drawn about the impact of classical $H_1$ blockers on the driving performance of allergic rhinitis patients on the basis of the impact in normal healthy volunteers of sedating antihistamines on behavioral skills considered important for driving (2). The interpretation of these data from the testing of psychomotor capabilities, which include extended attention span, vigilance, visual tracking, rapid information processing, and reaction time, is not possible when the effects of the disease symptoms per se on cognition and performance are largely unknown (3). What is truly germane is whether or not, to what extent, and in what manner the target disorder has an impact on the sufferer and the subsequent effects that medications have on the performance of the patients, not normal subjects. Unfortunately, because Dr. Bornstein and Ms. Yang were not able to use patients as their own control subjects, they could not definitively address these issues.

Genuine concerns about the potential negative effects of psychotropic medications continue (witness protests against the use of methylphenidate and neuroleptics at APA annual meetings). Our profession remains obligated to obtain a more comprehensive understanding of the impact of medications, but we can only evaluate these effects once we have learned more about the impact of the disorders themselves on performance.

There is an indication in the literature and, I believe, in the minds of practitioners that some medications have beneficial effects on overall performance. The regular use of antiepileptic agents, for example, appears to diminish the relatively increased risk for traffic accidents noted in people with epilepsy (4). The acute use of β blockers has been well-established as an effective treatment for performance anxiety in public speakers and musicians (5). Implicit in this utilization of β blockers is the belief that performance anxiety is a state which adversely affects cognitive and psychomotor performance. The negative effects of β blockers on performance may only pertain to cardiac patients who are normal in terms of concomitant anxiety.

To determine the true effects of drugs on neuropsychological performance and behavior, one must conduct placebo-controlled serial studies in patients while they are symptomatic and asymptomatic, with and without medications. In the case of disorders such as Tourette's disorder, which is usually associated with a lifelong course, the study by Dr. Bornstein and Ms. Yang of parallel patient groups differing only in terms of pharmacotherapy represents a feasible and practical alternative.

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## PTSD and Risk of Suicide

Sir: Herbert Hendin, M.D., and Ann Pollinger Haas, Ph.D. (1) reported an informative study of attempted suicide and preoccupation with suicide among a group of military veterans referred to them on the basis of combat experience in Vietnam and suspected posttraumatic stress disorder (PTSD). However, their observation that three of the 100 veterans in the group with confirmed PTSD committed suicide during the study, presented without comparison to an appropriate control group, provides questionable support for the authors' stated conclusion that PTSD poses a considerable risk of suicide. Does the reported frequency of suicide among Vietnam combat veterans with confirmed PTSD surpass or fall short of the frequency that would be observed in a comparison group of Vietnam combat veterans without PTSD, given that the two groups of veterans have similar prevalences of drug and alcohol abuse and other psychiatric or social risk factors for suicide that may coexist with PTSD?

Dr. Hendin and Dr. Haas also reported that numerous studies have shown a consistently higher risk of suicide among Vietnam veterans, ranging from 11% to 65%, than among nonveterans of the same age. However, the upper limit of this range of risk assessments is based on a problematic comparison of the mortality experience of males who were draft-eligible to that of males who were draft-exempt as a result of the military draft lotteries of the years 1970–1972 (2). During the early 1970s, shifts in the composition of the military toward an all-volunteer force, even among ground combat forces, cast doubt on the suitability of draft eligibility as a proxy for service in Vietnam (3). The reported 65% excess of suicides among the draft-eligible males cannot be attributed to Vietnam experience in the absence of information about where, or even whether, these males served in the military.

Although the results of other studies cited by Dr. Hendin and Dr. Haas indicate that Vietnam veterans are at higher risk for suicide than other veterans or nonveterans of similar age, the Vietnam veterans' risk was generally less than 25% higher, a modest difference in terms of epidemiologic risk assessment (4). In the largest study conducted to date, which was not cited by Dr. Hendin and Dr. Haas, Veterans Administration researchers found a 7% lower risk of suicide among Vietnam veterans than among veterans who served elsewhere during the Vietnam era (5).

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## Dr. Hendin Replies

SIR: Our study enabled us to show that guilt over actions in combat was the most significant factor distinguishing veterans with PTSD who became suicidal from those who did not. We are in no position to confirm or refute epidemiological studies on the overall incidence of suicide among Vietnam veterans. Our mentioning that three of our patients in the suicidal group did kill themselves in the course of the study simply suggested that we were dealing with a population at risk. No conclusions were or could be drawn from that fact.

The weakness in the epidemiological studies cited by Dr. Pollock is that they ignore the observations of most clinicians that those at risk for suicide are not simply Vietnam-era veterans, or those who served in Vietnam, but those who after intensive combat experience developed PTSD. Only an epidemiological study focused on this group can address that question. Our study did not attempt this but, rather, sheds light on which of the Vietnam combat veterans with PTSD are likely to be suicidal and why.

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## The Dissociative Experiences Scale

SIR: The Dissociative Experiences Scale has been used as a measure of dissociation in a number of articles published in the *Journal* (1, 2). The questionnaire seems to be becoming a recognized tool in modern psychiatric research. It is worth reviewing the original validation paper by Bernstein and Putnam (3) to see whether this self-report questionnaire merits such faith on the part of its users.

Bernstein and Putnam reported in their 1986 paper that the questionnaire was given to small groups of patients with various diagnoses (for example, posttraumatic stress disorder, multiple personality disorder, phobias, and schizophrenia) and to groups of normal adults and adolescents. In a scatterplot graph included in the paper, one sees that the scatter of scores is very wide in all groups except normal adults. Thus, for example, the scores of the adolescent group overlap with the lower 50% of the scores of the multiple personality disorder group. Although the median values for each of the groups were significantly different statistically, it is obvious that the questionnaire cannot be used, as the authors claimed, "to differentiate between subjects with and subjects without dissociative disorder."

The test-retest reliability was 0.84. This figure has now been cited (5 years later) by Barbara Sanders, Ph.D., and Marina H. Giolas, M.A. (2) to strengthen their conclusions that level of dissociation correlates with degree of childhood trauma in adolescent inpatients. However, the test-retest reliability was measured using only 12 adults and 14 adolescents; I can see no reason to expect that clinical groups will complete the questionnaire with the same reliability, yet this was not tested.

The article by James A. Chu, M.D., and Diana L. Dill, Ed.D. (1), again on the subject of dissociation and childhood trauma, pointed out that "one-quarter of the sample [inpatients] . . . had symptom scores at or above . . . the established median score of patients diagnosed with PTSD." It is worth reminding ourselves that "the established median score" was obtained in the validation study using only 10 Vietnam veterans who were taking part in another study. Is this score "established" because it is valid or because it is 5 years old and people have forgotten how it was arrived at? Based on these creaking foundations, conclusions are now being made about the degree of trauma to which abuse victims have been subjected.

Dr. Chu and Dr. Dill also concluded that dissociative disorders are being underdiagnosed, because they obtained high scores from a group of female inpatients that did not contain a high proportion of dissociative diagnoses. However, nobody seems to be concerned that the Dissociative Experiences Scale might be measuring something other than dissociation. All of the questions in the instrument are scored in the same direction, so that someone who had a tendency to say yes to any question (a distinct possibility with multiple personality disorder) would score high.

A measure of dissociation would be very valuable, but I suggest that more effort is required to validate and refine the Dissociative Experiences Scale before it is added to a growing list of research instruments that researchers unquestioningly accept as reliable and valid.

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## Drs. Putnam, Chu, and Dill Reply

SIR: The questions raised by Dr. Wiener concerning the validity of the Dissociative Experiences Scale are based on a very narrow reading of the literature available on this instrument. The scale has been used in over 20 scientific studies published in refereed journals, including six studies in this journal. Three studies (1–3), specifically conducted as replication studies, reported results very similar to those of the original validation study, and several other studies reported replication of the findings of the original study as applied to specific diagnostic groups. Dr. Wiener expresses concern that the median PTSD score used by Drs. Chu and Dill was based on data from only 10 Vietnam veterans. Currently, there are one published study and two studies in press, involving in excess of 100 combat veterans, that replicate the original findings. The Dissociative Experiences Scale was also included in the National Vietnam Veterans Readjustment Study, and data on its predictive validity for PTSD have been presented at national scientific meetings.

The test-retest statistic criticized by Dr. Wiener has been replicated by us on several occasions; e.g., our test-related Spearman correlation at 1 year is 0.78 in a sample of 83 mothers participating in an ongoing study of sexually abused children. Dr. Wiener's concerns about the relatively high scores of adolescents reflects lack of awareness of the developmental roots of dissociation. Dissociative Experiences Scale studies that have looked at this issue find a significant negative correlation of scale scores with age. This pattern is also true for studies of hypnotizability, a strong correlate of clinical dissociation, and for studies of the frequency of depersonalization symptoms in adolescents and adults. Children and adolescents are normatively more dissociative than adults, and their scores on the Dissociative Experiences Scale reflect this.

Bernstein and Putnam have never claimed that the Dissociative Experiences Scale is a diagnostic instrument and specifically cautioned against this use in the original validation article. However, the instrument does have very good discriminant validity for dissociative disorder diagnoses. For example, a recent multicenter study of 1,340 subjects found that the Dissociative Experiences Scale blindly categorized patients correctly into dissociative disorder and nondissociative disorder groups 85.5% of the time. This is an excellent performance for a simple 28-item, self-report questionnaire.

In summary, the Dissociative Experiences Scale has proven extremely useful for screening psychiatric populations for dissociative patients, for quantifying the contribution of dissociation to behaviors such as self-mutilation and suicidality and disorders such as PTSD, for investigating potential neurobiological mechanisms of dissociation, and for the epidemiological study of dissociation. The validity of the scale rests not on "creaking foundations" but, rather, on an increasingly broad international base of clinical investigation that spans many scientific disciplines. In our efforts to support researchers and clinicians interested in dissociation, we will continue to investigate the psychometric properties of the Dissociative Experiences Scale, to offer periodically updated information on it, and to consult with researchers using this instrument. French, Spanish, Dutch, and Cambodian language versions are available on request.

The limitation on references in letters to the Editor precludes complete documentation of the points we have made. We will gladly send any interested reader a fully referenced version of this letter.

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## Dr. Sanders Replies

SIR: In responding to the issues raised by Dr. Wiener, our own research with the Dissociative Experiences Scale provides considerable reassurance concerning its reliability and also some degree of assurance regarding its validity. The findings cited here were presented in two separate papers (Pitblado and Sanders, 1991; Giolas and Sanders, 1991) at the 8th International Conference on Multiple Personality/Dissociative States in Chicago in November 1991. The following is a summary of these studies.

In the research conducted by Colin Pitblado, Ph.D., and myself, 46 undergraduate students at the University of Connecticut were given the Dissociative Experiences Scale on two occasions 6–8 weeks apart. Their scores on the two occasions had a correlation of 0.79. Odd- and even-numbered items from the first administration of the scale were scored separately to permit calculation of a split-half reliability coefficient for the same subjects. The resulting coefficient was 0.93. The corresponding coefficient from the second administration was 0.97. To assess the effect of a longer time between administrations, odd-numbered and even-numbered item versions of the Dissociative Experiences Scale were prepared and presented to 16 undergraduates at Teikyo Post University. These students were given one version of the scale near the beginning of a semester and the other at the end of the semester, approximately 11 weeks later. The correlation between these sets of scores was 0.90, indicating substantial stability for performance, controlled for familiarity with individual items.

The validity issue was addressed by Marina Giolas, M.A., and myself in an experimental investigation of the experience of pain in high- and low-dissociating female college students. Forty-eight women who scored above 20 on the Dissociative Experiences Scale were selected for the high-dissociation group, and 48 who scored below 20 constituted the low-dissociation group. High dissociators showed a significantly greater tolerance for ischemic pain than did low dissociators. Moreover, across both groups, Dissociative Experiences Scale scores were correlated significantly, albeit modestly, with within-subject differences in ratings of sensory pain and ratings of emotional suffering associated with the pain. In other words, women with higher scores on the Dissociative Experiences Scale tended to be less bothered by sensory pain than women with lower scores. These results constitute the first experimental validation of the Dissociative Experiences Scale in which a behavioral criterion of dissociation was used.

In addition to our own findings, two large-scale studies that replicated and extended Bernstein and Putnam's 1986 results have been published by other investigators (1, 2). Clearly, additional psychometric research with the Dissociative Experiences Scale is needed; however, the results obtained so far indicate that the newly developed scale is a useful measure of dissociation in both clinical and nonclinical populations.

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## Failure to Use ECT in Treatment of Catatonia

SIR: The case report by Jeffrey D. DeLisle, M.D., "Catatonia Unexpectedly Reversed by Midazolam" (1), raised a number of clinical concerns. Over the years numerous treatments have been used in the treatment of catatonia, including thiopental sodium interviews, intravenous amobarbital, intravenous lorazepam, neuroleptics, bromocriptine, dantrolene, and ECT. The brief clinical vignette failed to mention the unique role that ECT plays in the reversal of catatonia of any origin. The APA task force report of 1990 (2) endorsed ECT as an effective treatment for the catatonic subtype of schizophrenia. In addition, case reports of organic catatonia (3) as well as lethal catatonia (4) indicate a common therapeutic pathway in the reversal of this potentially lethal state.

The omission of discussion of ECT in this case report is of concern. Practitioners should be advised to pursue treatment of catatonic patients with ECT, as the psychopharmacologic options appear quite limited.

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SIR: Dr. DeLisle described a case of catatonia in which midazolam elicited transient relief. He failed to discuss the inadequate treatment of this patient, possibly because *DSM-III* restricts treatment options.

Catatonia developed in a patient suffering from schizophrenia when she discontinued her medication. She required gastric intubation, and when she was given midazolam for anesthesia, she "began conversing loquaciously in an appropriate though tangential and delusional vein." She was repeatedly given midazolam and loxapine, so that "her catatonia improved, but her psychotic symptoms did not. A week later she began refusing all medication, suffered a partial catatonic relapse and worsening of psychosis, and went on to a prolonged course of illness." The report is presented as an example of the resolution of catatonia with midazolam when lorazepam had not been successful. In this description, the author encouraged the belief that benzodiazepines are useful agents in resolving catatonia, a belief that is poorly founded in the literature.

What is missing in this story is the effective treatment of the patient. Catatonia is remarkably responsive to ECT. Did the author fail to use ECT because the diagnosis was schizophrenia, a condition that is erroneously acknowledged as unresponsive to ECT? If so, the case is another example of the tragic consequences of the rigid classification inherent in *DSM-III.*

ECT has been described as effective for catatonia, in any of its expressions and forms, since the first cases of Meduna in 1934 and Cerletti in 1938. While *DSM-III* acknowledges catatonia only as a modifier of schizophrenia (diagnosis 295.2x), the literature is filled with extensive examples of catatonia appearing in patients with mania, depression, infections, endocrinopathy, and neurotoxic syndromes, as well as schizophrenia, and being responsive in each syndrome to ECT.

A colleague and I (1) recently argued that catatonia should be considered a separate class, distinct from schizophrenia, in *DSM-IV.* Such a reclassification would have encouraged the physicians treating this patient to introduce ECT at the earliest opportunity, allowing the patient to recover from the acute relapse.

REFERENCE

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## Dr. DeLisle Replies

SIR: I am grateful to Dr. Masiar and Dr. Fink for the opportunity to expand my thoughts on this complicated case. Several factors made the use of ECT in Ms. A's case impossible. First, the patient was both incompetent to give informed consent and refusing treatment. Second, she was being treated in a psychiatric unit in a remote and rural area that lacked the necessary medical amenities such as cardiac and oxygen monitors and anesthesiologists. Court-authorized transfer to another facility would have consumed time, and the accepting facility had at least temporarily refused her admission because of the gastrointestinal bleeding. By the time preparations for ECT could have been made, the patient was no longer catatonic, and the indication for ECT had passed. This example highlights the fact that many psychiatrists and their patients, especially in rural areas, lack access to this potentially life-saving treatment.

I heartily concur with Dr. Masiar and Dr. Fink that catatonia is poorly treated by the usual methods used for schizophrenia. While I do not dispute that ECT is an effective treatment for catatonia, I take exception to Dr. Fink's assertion that "the belief that benzodiazepines are useful agents in resolving catatonia . . . is poorly founded in the literature." In Ms. A's case the catatonia had resolved with midazolam and later with high doses of lorazepam; her partial relapse occurred only after she began refusing medication. The many case reports and small series reported in the literature, including the ones I cited, show that dramatic clinical improvements have occurred in many different patients given parenteral or high oral doses of benzodiazepines.

It is also noteworthy that intravenous barbiturates have successfully reversed catatonia, albeit temporarily (1, 2). Given the role of intravenous barbiturates in ECT induction, it is reasonable to query whether the clinical success of ECT in catatonia is due to the induction or the convulsion and, in any case, whether there is a shared mechanism of action. A 1953 study comparing catatonic patients who received ECT, thiopental sodium, or both showed equal improvements in all groups (2). More recent studies of sham ECT versus actual treatment demonstrate the clear superiority of the latter in depressed patients, but these results do not necessarily apply to catatonia, which has never been studied with sham ECT. As Sackeim remarked in a review of the subject, "There are no grounds as yet to determine whether the mode of action of ECT is the same or different in the various conditions for which it is effective" (3).

Even though these unanswered questions about ECT should give its proponents pause, with our current state of knowledge, ECT seems to be the most reliable treatment for catatonia. Still, the empirical successes achieved by benzodiazepines warrant serious attention and, in the face of failure or unavailability of other options, deserve a place in the therapeutic armamentarium. If more rigorous studies prove that benzodiazepines are efficacious in some catatonic patients, this treatment would have the advantages of rapidity and ease of administration, decreased risk from anesthesia, possibly fewer cognitive side effects, and greater acceptance by patients.

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## Autism Syndrome as a Final Common Pathway of Behavioral Expression for Many Organic Disorders

SIR: The article "The UCLA-University of Utah Epidemiologic Survey of Autism: The Etiologic Role of Rare Diseases" by Edward R. Ritvo, M.D., and associates (1) helps to reestablish a path of progress toward understanding autistic behaviors. The verification of the coexistence of autism and organic CNS disorders is a very important finding; however, the implication that this is a new or novel finding is misleading, as many historical works have pointed to this conclusion. Work done at the University of Utah from 1965 to 1978 clearly demonstrated the presence of organically based learning defects in autism (2), and our 1976 study of reports of neuropathology in childhood psychosis and autism clearly documented an extensive literature indicating various CNS pathologies in these disorders (3).

The field of research into childhood psychoses has been in scientific disarray for over 100 years due to a binary thinking process in which an organic disease condition and a childhood psychosis or autism syndrome are seen as mutually exclusive. The basic polemic has been that these aberrant behavioral syndromes are either organic diseases or they are psychosis, autism, dementia infantalis, etc. The truth is that organic disturbance and autistic syndromes of behavior go hand in glove with each other, and they are mutually *in*clusive, not mutually exclusive. We believe that an error in diagnostic conceptualization has occurred, because historically the presence of CNS pathology has been used to *exclude* the diagnosis of a childhood psychosis or autism.

Kraepelin (1896) based his system of nosology on the assumption of no known external organic causes, and this criterion of exclusion strongly influenced de Sanctis (1905) and Heller (1908) in their pioneer efforts to delineate childhood psychosis syndromes. It is notable that both of these authors specified "no neurological abnormality" (in parallel with Kraepelin) as part of their diagnostic criteria. Thus, the binary concept of mutual exclusivity between childhood psychosis and organic disease had been drawn.

This polemic tension existed in the mind of Sancte de Sanctis himself, and his writings reveal that on separate occasions he would oscillate between inclusion and exclusion of a case, depending on the coexistence of a known organic disorder. In some of his writings he wondered whether his "dementia praecocissima" could spring from the substrate of certain mental retardation or encephalitis cases. Nosology wars between dementia praecocissima (1905) and Heller's syndrome (1908) raged in Europe until 1958, when C. de Sanctis and G. Bollet attempted to document finally the nature of these syndromes and the assignation of the proper historical credits to each school (4).

Meanwhile, in America and Europe, Heller's syndrome was being written out of existence because of the discovery in neuropathological studies that the majority of these cases were due to conditions such as cerebral lipidoses, tuberous sclerosis, encephalitis, and other abnormal findings. In similar fashion, dementia praecocissima was abandoned as Cappon (1953) declared that the syndrome was related to a "heterogeneous ensemble of organic defects" such as Tay-Sachs disease, aphasias, etc. In America, Kanner (1943) started a replay of the European cycle with the concept of autism as a separate entity "without regression and evidence of organic defect."

In conclusion, we believe the literature clearly supports that 1) autistic behaviors are a final common pathway of multiple CNS neuropathologies (3), 2) autism and childhood psychosis syndromes are perfectly compatible with concomitant CNS neuropathological diagnoses, and 3) descriptions of behavior cannot be used to define or isolate CNS neuropathologies.

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LINCOLN CLARK, M.D.
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## Dr. Ritvo and Ms. Ritvo Reply

SIR: We did not imply that the article contained a "new or novel" finding, and we are surprised that Dr. Darby and Dr. Clark made such an inference. Indeed, we began publishing data in 1965 to support the hypothesis that autism is due to brain dysfunction (1). We reviewed the field and presented our ideas in detail in 1968 (2).

We wholeheartedly agree with Dr. Darby and Dr. Clark that our field has been in "scientific disarray" because of "binary thinking." For example, the word "psychoses" has had several distinct meanings. First, it has been used to refer to a group of illnesses, the psychoses (e.g., schizophrenia, manic-depressive disorder). Second, it has been used in a psychodynamic framework to refer to conditions in which reality testing is faulty (e.g., acute stress-induced regressive state). Third, it often is used to imply etiology—either organic or nonorganic, depending on the user's preference.

A different piece of semantic confusion was caused by the use of the term "autism" as both an adjective (by Bleuler and Kanner initially) and a noun (Kanner's later use and *DSM-III*) (3) to refer to a disease. Thus, a matrix exists for multiple uses with different meanings.

We agree with Dr. Darby and Dr. Clark that these confusions should be relegated to the past. The consensus now is that autism is a behaviorally defined syndrome; it can be caused by one or more types of brain pathology that, in turn, can have one or more causes.

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EDWARD R. RITVO, M.D.
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## Need for Integrating Environmental and Biological Factors in Psychiatry

Sir: The article by David Reiss, M.D., and associates on genetics and psychiatry (1) was impressive indeed, and I congratulate the *Journal* for highlighting it. The authors documented how the available data show not only the promise in studying a biological etiology for severe mental disorders, as has been claimed, but the promise in pursuing environmental factors as well. The article provided an excellent and concrete example of how the style of thinking the authors corrected, the style predominant at this time, can corrupt the scientific effort being made. Of course, predominant conceptual styles in any era can distort data in a way that has the same impact. We are accustomed to seeing some of the past excesses in deemphasizing less popular domains that were common to another orientation—psychoanalysis—during its dominance.

However, in any period it is difficult to get a perspective on current thinking. The goal, of course, is not the dead end of being "anti" any legitimate domain—not antibiological, antipsychological, or antisocial—but of psychiatry's becoming a field that truly attempts to attend to all three areas, an effort that is far more difficult than it seems and that continues to elude us. Our tendency, rather, is recurrently to "accept" all three domains, but with a kind of tolerating de-emphasis of the nondominant areas that prevents a truly multidisciplinary effort from being achieved. The report by Dr. Reiss and associates took a major step in redressing this error, an error that constantly threatens to rob our field of one of its most exciting and challenging potentialities: the possibility of bringing together the various domains to provide a total picture.

To the effort being made by the authors, three further steps might well be added. The first step is to undo another tendency that has grown in recent years, the tendency to amalgamate the psychological sciences and the social sciences in one mass, as reflected in the word "psychosocial." This amalgamation does with those fields what we have done in the past with biology: it reduces them in importance and undervalues their complexity.

The second step is to suggest that beyond the "partnership" the authors recommend, the biological, psychological, and social sciences might even better aspire to some sort of integration of findings and synthesis of theory. Not only does each domain need to be respected and developed, but the nature of their interaction needs to be clarified—truly an exciting challenge, which, in fact, Dr. Reiss and his colleagues have begun.

Finally it will also be important to notice the impact of our current style of thinking not only on research and treatment but also on education. By de-emphasizing the psychological and social aspects of the triad, we have driven many with training in those disciplines from focusing on mental disorders and discouraged many college students with interest in those areas from going into medicine and psychiatry.

The report by Dr. Reiss and associates is a gift to our field. I hope we will learn from it and see many more that drive this effort even further.

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JOHN S. STRAUSS, M.D.
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## Comorbidity of Attention Deficit Hyperactivity Disorder and Other Disorders

Sir: In the lengthy review article "Cormorbidity of Attention Deficit Hyperactivity Disorder With Conduct, Depressive, Anxiety, and Other Disorders" by Joseph Biederman, M.D., and associates (1), only by one word in the Conclusions section is attention deficit disorder in adults mentioned. At the very least, this article by pediatric psychiatrists should have had the words "in children" in the title.

Even if attention deficit disorder is recognized in *DSM-III* only as "residual" in adults, lack of mention in this article was a serious omission. Adult attention deficit disorder was discussed at length in a 1979 book (2) as well as lately in the pages of this journal (3). Attention deficit disorder in adults is a regrettable affliction that, among other things, coexists with the aftereffects of attention deficit disorder in childhood, such as low self-esteem and social fears.

The symptoms in adults are often identical to those in children. Instead of troubles in school, the adults have troubles on the job. Instead of being awkward in the gym, they drop things, bump into them, and get lost while driving. Since imipramine helps enough to enable them eventually to have remedial training (guided by neuropsychological testing) and psychotherapy to repair the self-image, it is essential that the condition be better known. The symptoms described in the article by Dr. Biederman and associates are not merely coexistent; many of them are caused by attention deficit disorder, as the therapeutic test demonstrates. Furthermore, people suffering from severe attention deficit disorder are often misdiagnosed as manic-depressive or schizophrenic, very much to their detriment (4).

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LEOPOLD BELLAK, M.D.
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SIR: The article by Dr. Biederman and associates allows another interpretation of the data. A hereditary triad of overreactivity, lability, and impulsivity, developing in different environments, may present as many diverse clinical pictures. The three traits are common to all, but there may be many different behaviors. All of them— impulsive eating, explosive temper, acting before thinking, inability to stick to plans, overdramatization, etc.—represent impaired self-control. These patients also have depressive symptoms, not because of depressive illness but because being discouraged is an appropriate response to their life situation.

Over 20 years of clinical experience in the psychopharmacotherapy of these conditions has clearly shown that the specific symptoms do not predict drug response, but the basic triad predicts that there is a 90% chance of a positive response to a small dose of one of the antidepressants. The response is immediate. Side effects are rare because of the small doses. There is rapid relapse on discontinuation. A patient's response to antidepressants does not warrant the assumption that one is treating depressive illness. The dose is one-tenth to one-third of the usual dosage for treating depression. Some unknown but different mode of action is involved. There is temporary control, not cure, as with insulin for diabetes.

Research is needed on the difference between amitriptyline and imipramine responders and between trazodone and amoxapine responders. Our preoccupation with specific behavior keeps leading us astray. The National Institute of Mental Health catchment area studies report that 12% of the adult population suffers from these disorders.

HANS R. HUESSY, M.D.
*Burlington, Vt.*

SIR: I read with interest the article by Dr. Biederman and associates on comorbidity with attention deficit hyperactivity disorder. I believe that it highlights the importance of identifying comorbid disorders with regard to the clinical treatment of and future research on this common childhood disorder.

In their study, however, the authors may have left out another comorbid disorder. The association of hyperactivity and attentional difficulties in encopretic children was observed by Levine (1). He described children with attention deficit as "task impersistent," seldom finishing anything they start, including defecation. Thus, some of them may have incomplete bowel movements, become gradually constipated, and thereby increase their susceptibility to developing encopresis. Boon and Singh (2) stressed the importance of assessing and treating comorbid disorders such as attention deficit hyperactivity disorder in the successful treatment of encopresis. A review of 30 inpatients with encopresis in the children's psychiatric hospital where I work showed that 11 (37%) had the diagnosis of attention deficit hyperactivity disorder.

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FRANKLIN BOON, M.D.
*Richmond, Va.*

SIR: I enjoyed the article on comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. The article, however, left me with the impression that different types of attention deficit hyperactivity disorder develop differently, mostly because of different brain physiology factors.

I think it is important also to consider that while attention deficit hyperactivity disorder may be present from birth, possible comorbid disorders may develop subsequently because of nonphysiological influences to which the child is exposed, especially including whether the attention deficit hyperactivity disorder is recognized early enough by parents or physicians and is treated or not. It has been my impression over the past 20 years of my clinical child psychiatry practice that if attention deficit hyperactivity disorder is diagnosed and treated early, then there are fewer conduct problems, depressive disorders, anxiety problems, and learning disabilities.

I feel that there are very important clinical applications related to the possibility that attention deficit hyperactivity disorder may be a prime etiological factor in a number of other emotional disorders. There are also very powerful financial aspects, such as the fact that certain insurance companies will not pay for the diagnosis and treatment of attention deficit hyperactivity disorder, whereas they will pay for the diagnosis and treatment of possibly more serious emotional disorders, although more serious emotional disorders could have been prevented had the attention deficit hyperactivity disorder been treated earlier.

As a child and adolescent psychiatrist, I have always been puzzled that there has not been more of a fuss made over the possibility of a connection between one of the most commonly diagnosed child psychiatric disorders, attention deficit hyperactivity disorder, and the most commonly diagnosed adult psychiatric disorders. I very much hope that the article by Dr. Biederman and associates will help contribute to a greater interest in the field of attention deficit hyperactivity disorder and how it is connected to other disorders that psychiatrists are called upon to treat. Perhaps we can even prevent these disorders more easily if we treat attention deficit hyperactivity disorder earlier.

DIRK E. HUTTENBACH, M.D.
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SIR: In their review of the comorbidity of attention deficit hyperactivity disorder with other disorders, Dr. Biederman and associates did not mention the high incidence of attention deficit hyperactivity disorder often reported in children with type I neurofibromatosis (1). An adult with type I neurofibromatosis and residual attention deficit disorder was recently treated at our medical center, reinforcing the importance of being aware of comorbidity factors for attention deficit hyperactivity disorder in adults.

Mr. A, a 25-year-old man, presented during his first week of basic military training with severe anxiety and suicidal ideation. After arriving at the training base, he had disturbing memories and dreams about a family member's death from a medical illness and also experienced four transient visual hallucinations of the deceased family member.

Mr. A had been given methylphenidate at age 6 for "hyperactivity." This medication was stopped at age 12, when his symptoms resolved. His family history included a seizure disorder in his father. His work history was striking; he had lost nearly 20 different jobs since graduating with fair grades from high school.

After admission, Mr. A's mood improved, and no further hallucinations occurred. His affect, however, seemed blunted for nearly a week after his initial presentation. Physical examination on admission had revealed numerous café au lait spots on his trunk and proximal extremities (which the patient said were "birthmarks"), axillary freckling, and a single small "buttonhole" lesion on his lower back. Dermatology consultation confirmed our diagnosis of type I neurofibromatosis through several tissue biopsies. Neuropsychological testing was obtained to evaluate for cognitive deficits secondary to the diagnosed disorder, and the results were consistent with mild residual attention deficit disorder.

Subsequent collateral history from Mr. A's mother revealed that his estranged father's seizure disorder resulted from an intracranial mass secondary to type I neurofiromatosis. Prior to Mr. A's discharge, he was educated about the implications of residual attention deficit disorder for job training and performance and was given genetic counseling regarding type I neurofibromatosis. Follow-up for treatment of his attention deficit disorder and for surveillance of the neurofibromatosis was arranged.

The patient's visual hallucinations, blunted affect, and chaotic, unstable job history required us to consider the possibility of prodromal schizophrenia. Transient visual images of a deceased loved one are not uncommon in nonpsychotic individuals undergoing severe stress, and Mr. A's blunted affect was not unlike that frequently encountered in basic trainees with severe adjustment disorders. His poor employment history, however, could not be explained by low intelligence or a personality disorder. A careful physical examination and medical evaluation helped explain this history with the more benign diagnosis of residual attention deficit disorder.

Residual attention deficit disorder in adults whose more striking hyperactivity symptoms resolved in childhood is increasingly recognized as a source of impairment and can be mistaken for thought or personality disorders (2). Heightened awareness of diseases such as type I neurofibromatosis that are comorbid with attention deficit hyperactivity disorder can help lead to appropriate diagnosis and intervention for adults as well as children.

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### Dr. Biederman and Dr. Newcorn Reply

SIR: Dr. Bellak raises the issue that our review of the literature was limited to reports on children. Since most of the available literature on this topic is limited to findings in children, our review took such a focus. We could not agree more with Dr. Bellak about the persistence, in many cases, of the syndromatic picture of attention deficit hyperactivity disorder into adulthood, and it is our belief that these comorbidities are likely to be found in studies of adults if such studies are undertaken.

Dr. Huessy proposes another interpretation of the findings reported in our literature review. While we do not agree with his hypothesis, we certainly welcome other points of view. For these points of view to be meaningful, they would also need to be subject to the same rigor as that used to back up the assertions presented in our review.

Dr. Boon raises the interesting notion of comorbidity between attention deficit hyperactivity disorder and encopresis. While we recognize that the former can coexist with a wide array of psychiatric, medical, and developmental disorders, our review was limited to those conditions about which a body of literature was available.

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JEFFREY NEWCORN, M.D.  
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### Response of Obsessive-Compulsive Disorder and Trichotillomania to Serotonin Reuptake Blockers

SIR: Case reports (1, 2), and one double-blind study (3) have suggested an association or linkage between trichotillomania and obsessive-compulsive disorder on the basis of positive responses of both disorders to serotonergic reuptake inhibitors such as fluoxetine and clomipramine. Swedo et al. (3) reported that 12 of 13 subjects responded to clomipramine in one study. We report the case of a 13-year-old girl with both obsessive-compulsive disorder and trichotillomania whose obsessive and compulsive symptoms responded to fluoxetine and to clomipramine, but whose trichotillomania responded minimally to each.

Anna, a 13-year-old girl, presented with a 3-year history of hair pulling (4–6 hours a day) and obsessive-compulsive symptoms (more than 5 hours a day of tapping, counting, and death images and a past episode of compulsive hand washing). Family circumstances included the father's past alcoholism, the mother's past bulimia, trichotillomania, and mild obsessive-compulsive symptoms, and other family history of depression, trichotillomania, and suicide. The patient's early developmental history included occasional extreme tantrums. She was sociable and academically average, but by the age of 10 she was seen as immature and anxious and was pulling out her hair, leaving bare patches and excoriations. Intermittent psychotherapy, one psychiatric admission, and brief treatment with fluoxetine did not alter the picture.

In the hospital Anna was started in an open treatment study of obsessive-compulsive disorder in which she took fluoxetine. The dose was increased over 2 months to 80 mg/day, which she continued to take for 3 months, with a gradual decrease in symptoms until she had no compulsions and 1 hour per day, or less, of obsessions, but there was no change in her hair pulling. Because of the latter, fluoxetine was tapered and clomipramine was begun and increased to 225 mg/day, with continued overall improvement in obsessive-compulsive symptoms over 12 weeks, but little change in her trichotillomania. After 14 weeks of clomipramine treatment, including 4 weeks at 200 mg/day or more, she began behavioral therapy specifically for the trichotillomania. After 8 months of clomipramine, 200 mg/day, Anna had marked improvement in her obsessive-compulsive disorder but no change in her hair pulling.

Trichotillomania has been seen as a compulsion, with increased tension prior to the act of hair pulling and a subsequent sense of release or gratification. Compulsions of obsessive-compulsive disorder are also associated with tension reduction, but not gratification. For this patient, there appeared to be an ego-syntonic, sensual, and kinesthetic quality in the experience of hair pulling that is not described for compulsions in obsessive-compulsive disorder. Not wishing to relinquish her hair pulling, she never benefited from behavioral therapy. Another distinction between obsessive-compulsive disorder and trichotillomania may be the person's awareness of the compulsive act, since the sufferer is painfully aware of the compulsion in obsessive-compulsive disorder, whereas the hair puller often describes an "absence," or dissociated state—something Anna often reported.

In conclusion, this case raises questions about whether obsessive-compulsive disorder and trichotillomania differ in process, function, and response and whether trichotillomanic compulsions can also be subtyped on these dimensions.

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*Reprints of letters to the Editor are not available.*

THE AMERICAN JOURNAL OF PSYCHIATRY
*Special Articles*

# Update on the Dementia Spectrum of Depression

V. Olga Emery, Ph.D., and Thomas E. Oxman, M.D.

*Objective: The primary focus of this review is to examine the usual dichotomy between depressive dementia as functional and reversible and degenerative dementia as organic and irreversible. Method: The authors propose viewing depression, cognitive impairment, and degenerative dementia as intersecting continua. They define five prototypical groups along these continua: 1) major depression without depressive dementia, 2) depressive dementia, 3) degenerative dementia without depression, 4) depression of degenerative dementia, and 5) independent co-occurrence of degenerative dementia and depression. Clinical, neuropsychological, and neurobiological studies comparing these groupings were identified by a computerized literature search covering the past 20 years. References were selected for review if they compared at least two groups. Degenerative dementia was limited to the Alzheimer type. Results: No studies clearly included all five of the prototypical groups. There are methodological problems with each type of research reviewed, but the consensus of the research is that severe cognitive impairment of depression is associated with a variety of organic abnormalities. Depending on the length of follow-up, depressive dementia may not be as reversible as previously thought. Conclusions: The continuum viewpoint encourages longitudinal clinical follow-up for early detection and alleviation of incipient depressive and dementing symptoms. Hypotheses of overlapping pathophysiological mechanisms rather than differential diagnosis become an important research focus. The authors discuss three different types of relationships for future research: 1) interactions, 2) consequences of disease or treatment, and 3) necessary but not sufficient pathophysiology.*

(Am J Psychiatry 1992; 149:305–317)

Disorders of mood are usually associated with cognitive impairment that can range from mild to severe. Mild cognitive impairment accompanying major depression raises little diagnostic or therapeutic uncertainty. When cognitive impairment dominates the clinical picture in patients with symptoms of major depressive disorder, issues arise that necessitate a framework for understanding and classifying these combined disturbances of mood and cognition. The major issue of concern is if and how depressive illness itself causes the severe impairment (i.e., depressive dementia) or if some form of degenerative brain disorder is present. Depressive dementia comprises a subgroup of a broader clinical phenotype called pseudodementia. Previous discussions of pseudodementia (1–3) have illustrated the importance of depressive dementia and tended to dichotomize it on the basis of irreversibility versus reversibility, structural versus functional, or organic versus nonorganic etiology. Questioning these dichotomies, we examined the relationship between depression and dementia from a historical perspective and developed a

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framework using continua to conceptualize illnesses where mood and cognitive disturbances coexist. Using available evidence from relevant clinical, neuropsychological, and neurobiological studies, we then evaluated the dichotomous versus continuous views of disorders of mood and cognitive impairment.

## HISTORICAL BACKGROUND OF THE DICHOTOMY VIEWPOINT

The attempt to differentiate between what have historically been considered "nonreversible" dementing disorders and reversible "dementia-like" disorders has a rich theoretical and clinical tradition. In the mid-nineteenth century, focus on irreversibility as a diagnostic criterion for dementia led to a need for a concept to designate contrasting, "reversible," broad-based cognitive deterioration. The term "vesanic dementia" was used through the 1880s to describe dementing syndromes that appeared reversible (4).

During the late 1800s, "vesanic dementia" was replaced gradually by Wernicke's term "pseudodementia." In 1898, Ganser described three victims of accidents who seemed to "mimic mental weakness" (4). Pseudodementia and the syndrome described by Ganser inaccurately became equated (5, 6). Pseudodementia is better conceptualized as an overarching class, of which Ganser syndrome and depression are only parts (6). Larger series of patients with dementia have revealed that the picture of dementia is approximated by patients with a variety of other neuropsychiatric conditions, including conversion disorder, deafness, delirium, drug effects, epilepsy, hypomania, depersonalization, malingering, normal-pressure hydrocephalus, and schizophrenia (3, 5–9). Although the frequency distribution of disorders approximating dementia remains unclear, what emerges with some clarity is that depressive-spectrum disorders constitute a substantial core in any series of patients with potentially reversible dementia.

Both historical definitions of pseudodementia and current-day case reports center on two characteristics: 1) appearance of organic deterioration of cognitive function and 2) reversibility—remitting of symptoms inconsistent with "true" degenerative dementia (9). In the past few decades, these two characteristics embodied in cross-sectional case series have led to a clinical emphasis on the search for curable presentations of dementia.

## HISTORICAL BACKGROUND OF THE CONTINUITY VIEWPOINT

Both historical and current clinical case series promulgated a dichotomous approach that viewed cognitive impairment as either organic or nonorganic but not both. The dichotomy between organic and nonorganic cognitive dysfunction in depressive disorder was first challenged by Mairet (10) with his conceptualization of "melancholic dementia" as organic. Mairet presented a series of cases of patients with melancholic dementia who showed both organic brain changes and reversibility. He observed that patients with melancholia were found to have changes in the temporal lobe on autopsy. Mairet's melancholic dementia appears essentially similar to depressive dementia as defined today (2, 4, 11, 12).

In 1948 Newton (13) reported that 42% of 76 postmortem brains from patients with affective psychosis demonstrated the neuritic plaques and neurofibrillary tangles associated with Alzheimer's disease. This was greater than the 25% of 24 postmortem brains of patients with schizophrenia that demonstrated plaques and tangles. In 1955 Roth (14) demonstrated that most hospitalized elderly patients with depression, with or without substantial cognitive impairment, did not develop dementia within 3 years. However, Roth et al. (15) also published a seminal paper promoting the use of quantitative assessment of degenerative changes: in a series of 300 autopsies of mental hospital patients, they found that 25% of those regarded as suffering "functional" psychoses showed degenerative changes of moderate or severe degree. Roth et al. concluded that this overlap was due at least in part to the co-occurrence of two disorders.

The association of depressive dementia with subsequent degenerative dementia has also been reported in longitudinal studies (3, 16–18). These studies have emphasized the diagnosis of depressive dementia because the patients responded favorably to antidepressant treatment. However, not all of the patients demonstrated complete or permanent improvement in cognitive impairment after treatment for depression, particularly with long-term follow-up. Bulbena and Berrios (4) reported a positive outcome for only 47% of 61 published case reports. These authors reported a 50% rate of negative outcome in their own series of 22 geriatric patients. Alexopoulos et al. (19) found that 38% of 37 psychiatric inpatients with late-life depression and severe cognitive dysfunction turned out to have degenerative dementia after the depression cleared.

Poor outcome appears to be related to the setting and length of follow-up. For example, Murphy (20) reported that 3% of 124 elderly patients with depression were demented at 1-year follow-up, and Rabins et al. (16) reported that 12% of 17 older depressed patients remained demented at 2-year follow-up. Reding et al. (21) reported that more than 50% of elderly patients diagnosed with depressive pseudodementia at a dementia clinic eventually demonstrated degenerative dementia at 3-year follow-up. Kral and Emery (17) found that 79% of 44 older patients with depressive dementia had developed a dementia syndrome with an Alzheimer phenotype in a 4- to 18-year follow-up.

Although these data suggest rethinking of old paradigms, methodological problems necessitate proceeding with caution. For example, the cross-sectional and longitudinal data cited span several decades. During this period of time there were criterion and definition changes for both affective and primary degenerative dementing disorders. Because of possible selection biases and limited information regarding original and follow-up diagnostic criteria, it is difficult to make comparisons across studies. Therefore, we regard the discussion that follows as heuristic in nature. Future research directions that will lead to greater clarification of the relationship between depressive dementia and degenerative dementia are outlined in the final section of this paper.

## CONTINUA OF DEPRESSION AND DEMENTIA

Consideration of variability in three different processes associated with aging may help to clarify the discrepant historical viewpoints and findings presented here. Although these processes fall along separate continua, we are particularly interested in their co-occurrence or intersection. We therefore describe these three continuous processes and several anchor points for the relevant interaction of these continua to help frame this research review. Each of these processes can be assessed by a variety of continuous measures. Defining a disorder or disease level is not a dichotomous decision. Most of the continuous measures are associated with suggested cutoff points or scores. However, the presence of disease is not as clear as the cutoff points themselves.

For the depressive axis, the separation of depressive symptoms from a depressive disorder is difficult, particularly in the elderly (22). Depressive symptoms are measured by a variety of instruments. Regardless of the instrument and its cutoff score, most community surveys reveal about a 15% prevalence of depressive symptoms in people older than 65 (22). This rate is not different from that found among middle-aged and younger adults. The "gold standard" for depressive disorder is a clinician-based interview. Surveys using this standard for major depressive disorder—the type of depression most likely associated with severe cognitive impairment (9, 12)—reveal rates of 1% to 5%, and the lowest rate is consistently found in subjects older than 65. Of the three age-related continua, this is the only one that is inversely related to age.

For the cognitive impairment axis, cross-sectional studies have shown increases of impairment with age. Longitudinal studies suggest that the degree of and age at impairment are quite variable and specific to the particular cognitive process examined (23). As with measures of depression, neuropsychological test batteries and brief mental status examinations are continuous measures with normal ranges and cutoff scores suggesting impairment. With education, sex, and differences in the form of the test accounted for, substantial declines in cognitive function occur with age, even in the absence of systemic disease (23). Also as with depression, the boundary between age-expected cognitive impairment and early primary degenerative dementia is not easily established (22, 24). Highly age-associated prevalence figures range from 1% at age 65 to 20% at age 86 or older (22, 25). For the degenerative pathology axis, cognitive performance in healthy subjects correlates with structural and functional measures of brain function (23). Age-associated structural changes in normal brains include selective regional neuronal loss, cerebral atrophy, senile plaques, and neurofibrillary tangles (26–28). Functional changes include changes in metabolism and neurotransmitter activity (29). These structural and functional changes vary continuously and are seen in both normal aging and dementia. The demarcation between normal aging and degenerative dementia is not easily defined. Although there are no standards for neuronal loss (28), atrophy (30), or neurotransmitters (29), several groups have suggested age-corrected cutoff scores for number of plaques and tangles necessary for diagnosis of Alzheimer's disease (26, 31).

We now describe five points along the depressive, cognitive impairment, and degenerative pathology axes to define prototypical groups, which, in different combinations, form the subject groups of the research review that follows.

### *Major Depression Without Depressive Dementia*

The first basic group is major depression with minimal or subclinical cognitive deficits. We are reticent to define this group as depression with no cognitive deficits because most research (32, 33) suggests that depression in persons over age 40 nearly always involves some cognitive disadvantage with respect to normal subjects. Poor performance on cognitive examination, allegedly because of poor effort from loss of interest and concentration, is one of the criteria for major depression in *DSM-III-R*.

### *Depressive Dementia*

The second prototypical group is major depression with cognitive deficits that reach clinical proportions, i.e., depressive dementia (3, 6, 12). The primary diagnosis is depression, and cognitive deficits are secondary to depression. As described by Folstein and McHugh (12), this type is an organic but "reversible" cognitive dysfunction, possibly due to factors associated with the pathology of mood disorder, such as brainstem neuronal dysfunction or biogenic amine deficiency. Thus far, it is possible to establish this type only retrospectively, after treatment of depression. In this review we consider the terms "depressive dementia," "depressive pseudodementia," "dementia syndrome of depression" (12), and "major depression with depressive dementia" as synonyms.

Age at first onset of depression is a potentially important characteristic often associated with family history, depressive delusions, treatment response, and cognitive decline. Some studies (34–36) have suggested that late-onset depression in older persons is associated with more medical and neuroanatomical changes and, therefore, greater risk of cognitive impairment or dementia. The evidence remains controversial, however, as to whether late-onset depression is associated with cognitive impairment greater than or equal to that of early-onset depression (37–39).

### *Degenerative Dementia Without Depression*

The third group is primary degenerative dementia (38) without depression. Reported frequencies of primary degenerative dementia without affective symptoms of any kind vary a great deal across studies, ranging from 50% to 100% (14, 40–42). This spread between rates is to a large extent a function of varying criteria for affective symptoms and other methodological variations, such as sample definition and sample selection.

The age at onset of degenerative dementia of the Alzheimer type, like the age at onset of major depression, is a potentially important characteristic often associated with neurobiological and clinical findings (43, 44). As with age at onset of depression, the evidence remains controversial, but results of comparisons of these prototypical groups may be influenced by age at onset.

### *Depression of Degenerative Dementia*

The fourth major point of reference on the axes is the presence of a dementing disorder with different degrees of depression. At issue is whether degenerative diseases of the brain, such as Alzheimer's disease, cause depressive illness or, rather, result in the kind of demoralization that can occur with any major illness. In most cases of this basic type, the primary diagnosis is dementia and depression is secondary. Criteria for a major depressive disorder are more difficult to establish for this type. *DSM-III-R* recognizes this difficulty by allowing for subcategorization of primary degenerative dementia with depressive features; a second axis I diagnosis is not required. Prevalence rates of depression in primary degenerative dementia range from 0% to 50% (40–42). As stated before, such a spread between reported prevalences is due mainly to variations in criteria for depression and other methodological differences.

A variant of this prototype is the dependence of both dementing disorder and depression on a common underlying neuropathology. Dementia may not have preceded the depression temporally. Examples of this type of dual presentation include vascular dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, HIV infection, and normal-pressure hydrocephalus. In cases where the symptoms meet *DSM-III-R* criteria for both dementia and mood disorders, multiple axis I diagnoses may be given.

### *Independent Co-Occurrence of Degenerative Dementia and Depression*

The fifth group of the typology involves co-occurrence of a degenerative dementing disorder and an independent, usually preexisting, recurrent depressive disorder. This type represents a confound for causal explanations of dependency between degenerative dementia and depression. We will address this issue in the course of presenting and interpreting relevant studies as part of the research review.

## REVIEW OF THE RESEARCH LITERATURE

To review published studies on the relationships of these five prototypes of varying degrees of affective and dementing disorders, we performed a computerized literature search covering the past 20 years. We examined the references listed in any articles and book chapters relevant to these relationships. No studies clearly included all five of the prototypical groups. Usually one or two groups were compared with a normal control group and/or with each other. References were selected for review if they compared at least two groups. The scope of this paper does not permit equal attention to all forms of degenerative dementia. Each form has its special issues, all of which cannot be dealt with in a single paper. Therefore, the main focus of this update is on the spectrum of depression and primary degenerative dementia of the Alzheimer type. Age at onset of both depression and degenerative dementia is important but difficult to determine. When studies provided this information, we noted it. For dementia, the best comparison with depression would be with mild rather than severe dementia. We also noted severity when specified.

### *Research on Clinical Features*

*Onset of illness.* A key variable of clinical history is onset of illness. Disease onset in primary degenerative dementia is insidious by definition (*DSM-III-R*). In a study of 124 patients, Zubenko (45) supported this definition by finding that an insidious course was the most common presentation of primary dementia regardless of etiology. Although Zubenko found that the onset of illness in 82% of patients with uncomplicated primary degenerative dementia was insidious, another 14% evidenced uncertain progression.

When depressive dementia is compared with primary degenerative dementia, the time elapsed between onset and seeking medical help is usually shorter (3, 9, 46). For example, Rabins et al. (16) reported a median duration of 2 months of symptoms for 18 subjects with depressive dementia compared with a median of 5 years for subjects with degenerative dementia. Reynolds et al. (47) also found a shorter median duration of cognitive impairment in patients with depressive dementia than in patients with primary degenerative dementia.

The overlap of symptom onset between depressive dementia and primary degenerative dementia is large. In the study of Rabins et al. (16), for example, the range of symptom duration in depressive dementia was 1 week to 6 years and the range in degenerative dementia was 5 months to 7 years. Onset and insidious development do not appear to be pathognomonic for either depressive or primary degenerative dementia.

*History of psychiatric disorder.* Another frequently described feature of the clinical history is previous personal or family psychiatric disorder. A history of previous affective disorder is reported more frequently in depressive dementia than in primary degenerative dementia (3, 16, 46). In an examination of psychiatric history, Rabins et al. (16) found a significantly higher frequency of previous depression in depressive dementia than in primary degenerative dementia—61% versus 6%. The frequencies of a family history of affective disorder in the two diagnostic groups were not significantly different.

In looking only at groups at one end of the spectrum—i.e., the difference between degenerative dementia with and without depressive disorder—Pearlson et al. (48) found an association between family history of affective disorder and depression. They found that 41 patients with primary degenerative dementia in their first episode of depression had significantly more first-degree and second-degree relatives who were depressed than did 71 nondepressed patients with primary degenerative dementia. Pearlson et al. suggested that depression in primary degenerative dementia is genetically related to primary affective disorder.

*Intrapsychic depressive symptoms.* Not surprisingly, in comparing depressive dementia with primary degenerative dementia, investigators such as Rabins et al. (16) reported that depressive dementia involved a higher frequency of current depressed mood and delusions. Similarly, Lazarus et al. (40) noted that patients with depressive dementia had higher scores on items assessing intrapsychic symptoms of depression such as helplessness, hopelessness, and worthlessness. Reynolds et al. (49) also reported that patients with depressive dementia had higher Hamilton Rating Scale for Depression scores for anxiety and loss of libido.

*Cognitive and vegetative depressive symptoms.* The "I don't know" answer is often associated with pseudodementia, as described by Wells (3), and the "near miss" answer, *vorbeireden,* is associated with primary degenerative dementia (50). This distinction has been questioned by Hendricks (51), who found that a "guessing response style" was used significantly more often by patients with primary degenerative dementia than was the "near miss" answer. Young et al. (50) and Emery (6) found that the "don't know" response was used frequently not only by patients with major depression but also by patients with primary degenerative dementia. Emery (6) noted that the "near-miss" answer depends on correct processing of a question; Alzheimer's disease appears to erode the capability for correct processing of questions.

A related clinical feature is behavioral consistency. When primary degenerative dementia is compared with major depression (52) or depressive dementia (3), behavior in degenerative dementia appears more consistent with apparent severity of cognitive dysfunction. For example, the patient with depressive dementia can find his or her way around a hospital when hungry or looking for a television set, but the patient with primary degenerative dementia cannot, irrespective of motivation. This behavioral measure has been empirically supported by Reynolds et al. (47), who found that patients with primary degenerative dementia had significantly more impairment finding their way when indoors or on familiar streets than patients with depressive dementia. Interestingly, Kahn et al. (52) reported that patients with concurrent degenerative dementia and depression had more memory complaints than patients with degenerative dementia without depression, even though their memory testing was better.

Perhaps most important with respect to complaints of memory is the finding by O'Connor et al. (53) that although depressed patients older than age 75 had the most memory complaints, more than half of community residents older than 75 with mild or moderate dementia also complained of memory problems, as did one-third of normal subjects. These results suggest that an older person's complaint of the presence of memory loss has limited diagnostic value.

Finally, sleep disturbance is an important vegetative symptom of major depression. As primary degenerative dementia progresses there is also a breakdown of the sleep-wakefulness cycle, as indicated by nocturnal wandering and daytime sleepiness (48, 54). However, Reynolds et al. (47) reported that patients with depressive dementia differ from those with primary degenerative dementia by having more severe early morning awakening.

### *Research on Neuropsychological Features*

There is a fairly large literature related to the neuropsychology of depression in general but less information relating to the neuropsychology of depressive dementia. A major problem with comparative studies is the lack of attention to the relative severity of dementia. Subjects selected for study of the dementia of Alzheimer's disease usually have a more obvious and severe dementia than subjects selected for study of major depression. Nevertheless, in studies of cognitive function that compare depressive dementia with both primary degenerative dementia and major depression, the most consistent finding is that there are more significant differences between major depression and depressive dementia than between depressive dementia and primary degenerative dementia (6, 12, 55).

*Memory.* Hart et al. (56) compared patients with mild degenerative dementia, normal subjects, and patients with major depression without depressive dementia and found that both the depressed and demented patients showed learning impairments but only the demented patients showed a significantly more rapid rate of forgetting after learning. These investigators suggested that memory was impaired in both disorders but that different psychobiological mechanisms were involved.

In a study of memory in age-matched patients with depressive dementia, primary degenerative dementia, and major depression without depressive dementia, Emery (6) found that the greatest deficit for patients with depressive dementia and for patients with primary degenerative dementia was in delayed recall. In comparing these same three types of patients, Speedie et al. (55) also found that patients with depressive dementia performed worse than depressed patients without dementia on tests of free recall, delayed recall, and verbal delayed memory but not on tests of delayed visual memory. All patient groups performed worse than normal subjects in both studies (6, 55).

Although the majority of comparisons have used patients with unipolar depression and degenerative dementia of the Alzheimer type, interesting and important distinctions are being reported regarding two other groups—patients with bipolar affective disorder and patients with subcortical dementias, a subgroup of degenerative dementias (57)—in a variety of different contexts. Dupont et al. (57) found that young patients with a history of bipolar affective disorder had a type of long-term memory deficit similar to that of patients with Huntington's disease.

*Language.* Turning to the higher cortical function of language, we found fewer data on depressive dementia than we did for memory. Speedie et al. (55) found that patients with depressive dementia were indistinguishable from patients with primary degenerative dementia on the number of items correctly named or on the speed of response. Similarly, Emery (6) found that there were no significant differences between age-matched patients with depressive dementia and primary degenerative dementia on language measures of repetition, confrontation naming, auditory word recognition, sequential commands, complex syntax, or reading commands. Depressive dementia and primary degenerative dementia were discriminated by a responsive speech task (e.g., "How many days in a week?") and a sentence completion task (e.g., "Roses are red, violets are what?"). Linguistically, these two tasks are among the simplest (58).

*Abstraction.* To investigate the cognitive domain of abstract reasoning, Cassens et al. (32) administered the Wisconsin Card Sorting Test to several groups of depressed patients. They found that patients with depressive dementia scored significantly lower than depressed patients without depressive dementia. These researchers concluded that the performance of patients with depressive dementia was similar to that of patients with organic dysfunction.

### *Research on Neurobiological Features*

*Neuropathology.* The average aged brain atrophies and weighs about 8% less than the average middle-aged brain. In degenerative dementia, the brain weighs about 20% less than the average normal middle-aged brain (26). Neuritic plaques and neurofibrillary tangles are the hallmark of Alzheimer's disease, but they are not specific to it. In fact, several investigators have reported that after age 80 there is substantial overlap between the brains of patients with degenerative dementia and those of age-matched normal subjects (59). To control for this high rate of overlap of neuropathology with age, the widely used Khachaturian diagnostic criteria for Alzheimer's disease (31) were devised by using an age-adjusted number of senile plaques per square millimeter in sampled microscopic fields.

Thus far, there have been too few autopsy studies of depressive dementia to make any definite conclusions. However, as already noted, some neuropathological studies have suggested an association between severe depression and the pathology of degenerative dementia. This may simply be the co-occurrence of depressive disorder in the context of the higher prevalence of primary degenerative dementia associated with age. However, there have been reports suggesting that degenerative dementia is more likely to occur in patients with depressive disorders than in patients with or without other psychiatric disorders. Brown et al. (60) reported that 62% of 29 patients with affective disorders, compared with 16% of 148 patients with schizophrenia, had primary degenerative dementia or vascular neuropathology. Kral and Emery (17) found that 79% of 44 elderly patients with depressive dementia developed primary degenerative dementia over a long-term follow-up. In nine of these patients studied postmortem, neuropathological examination revealed the typical markers of Alzheimer's disease: neuronal loss, neurofibrillary tangles, and neuritic plaques. Although other longitudinal accounts found smaller percentages of cases of depressive dementia with an ultimate course of primary degenerative dementia, the figures nevertheless appear much higher than the usual 5%–10% prevalence figures for degenerative dementia in the general population over 65 years of age.

A related neuropathological finding is the association of degenerative changes in subcortical nuclei in patients with degenerative dementia who have concurrent major depressive disorder. Zubenko and Moossy (61) and Zweig et al. (62) both reported neuropathological findings indicating the presence of more neurofibrillary tangles in the locus ceruleus, substantia nigra, and central superior raphe nucleus of patients with Alzheimer's disease who also had major depressive disorder than in subjects who did not have major depressive disorder. These findings suggest a subcortical pathological role for some depressive symptoms in Alzheimer's disease.

*Neuroimaging.* There are two basic kinds of neuroimaging methods: those which assess neuroanatomical structure (e.g., computerized tomography [CT] and magnetic resonance imaging [MRI]) and those which assess functional measures of the neural substrate (e.g., positron emission tomography [PET], regional cerebral blood flow [rCBF], and single photon emission scanning [SPECT]).

A substantial body of evidence reveals that CT-estimated tissue density decreases and ventricle size increases with age (30, 63). Some studies suggest that norms for the elderly with optimal health are different from those in subjects with a history of chronic medical diseases (30). It is also important to note that there may be different mechanisms for the occurrence of sulcal atrophy and for ventricular enlargement. Age-related changes in these measures do not correlate very highly.

In comparisons between normal elderly subjects and patients with primary degenerative dementia, a greater degree of generalized atrophy is seen in those with dementia (30, 35, 39). There appears to be a correlation between brain atrophy and severity of dementia, especially when variables such as education and intelligence are controlled for (35, 39, 64). Nevertheless, there exists considerable overlap in atrophy of brain tissue between age-matched normal subjects and persons with dementia (30). There have been attempts to find other CT scan measurements specific for degenerative dementia. To date, however, no CT or MRI neuroradiographic finding is pathognomonic for primary degenerative dementia.

A variety of CT abnormalities suggesting ventricular enlargement or tissue atrophy have also been observed in elderly depressed patients (35, 65). Brain CT and MRI studies have shown differences between late-onset and early-onset depression; late-onset depression has been found to be more comparable to primary degenerative dementia (22, 34–36).

In one of the few neuroimaging studies to specifically examine the dementia of depression, Pearlson et al. (39) compared normal subjects with three prototypical groups all older than 59 years of age. Measures of both ventricle size and CT attenuation (density) showed a consistent pattern of increasing abnormality from normal control subjects through patients with major depression without dementia to those with dementia of depression to those with degenerative dementia without depression. Many but not all of the depressed patients had early-onset depression, not late-onset depression.

Hyperintensities on MRI scans are an additional important but controversial structural finding related to aging, depression, and dementia. Many patients show white matter lesions on MRI scans that are not demonstrated on CT scans. These patients have a significantly greater incidence of cardiovascular risk factors than patients without white matter lesions. These hyperintensities are frequently but not exclusively found in multi-infarct dementia (66, 67). Although neither the differential diagnostic nor conceptual significance of these white matter lesions is understood at present, investigations of depressed patients are providing some intriguing findings. Alexopoulos (34) reported more frequent hyperintensities in depressed patients with onset of illness after 45 years than in patients with an earlier age at onset. Coffey et al. (68), using an MRI hyperintensity scoring system, noted mild periventricle caps or halos in all elderly normal control subjects as well as mild deep white matter hyperintensities in the majority of their normal subjects. In elderly depressed patients referred for ECT, the hyperintensities were more severe and subcortical gray matter nuclei were involved. Rabins et al. (36) reported a similar finding in patients with late-onset depression.

One final note regarding structural neuroimaging relates again to bipolar affective disorder. Along with the intriguing neuropsychological similarities between bipolar disorder and subcortical degenerative dementias, neuroimaging structural similarities between these disorders have been reported. In a large sample of younger patients, Andreasen et al. (69) demonstrated CT ventricular enlargement in patients with bipolar disorder that was independent of age, unlike the association between age and enlargement found in patients with unipolar depression. Similarly, Dupont et al. (57) reported that 47% of 19 young male patients with bipolar disorder demonstrated subcortical MRI hyperintensities involving white matter. None of their control subjects demonstrated these findings, and all seven of their patients with abnormalities who were available for 1-year follow-up still demonstrated the abnormalities. Long-term follow-up of these patients into later life will be most valuable.

At this point, it appears that structural imaging results, rather than discriminating between depression and dementia, point to some overlap if not association between geriatric depression and bipolar depression on the one hand and dementia on the other.

Of the three types of functional neuroimaging, PET has produced more consistent findings than rCBF or SPECT, so we limited our review to this modality (70, 71). In contrast to results from structural imaging, functional imaging with PET appears to suggest more characteristic differences between late-life major depression and primary degenerative dementia. Before discussing these findings, however, it is important to acknowledge some of the methodological problems that may influence clinical interpretations of studies using this complicated technology (72). These limitations include variations in mental activity of the subject during the procedure, the need for adjustment for focal atrophy, difficulties with consistent anatomical localization, and the necessity to adjust significance levels for the large number of statistical comparisons made with small groups of subjects. Given these limitations, primary degenerative dementia appears to have a characteristic pattern of glucose hypometabolism. The primary areas involved are the posterior parietal cortex, often with extension into adjacent temporal and occipital lobes and sparing of the primary sensorimotor cortex (73, 74). This temporoparietal pattern is found in most patients with primary degenerative dementia but not in patients with depression, patients with multi-infarct dementia, or healthy age-matched control subjects (73). However, the pattern has been reported in reversible normal-pressure hydrocephalus (74).

Cerebral metabolism is also altered in depression (75). Buchsbaum et al. (76) found a smaller anteroposterior gradient in glucose metabolism in depressed patients than in control subjects. The order of magnitude of the difference was similar to that between normal subjects and patients with multi-infarct dementia (77). In a series of studies, Baxter et al. (78, 79) found that younger patients with unipolar depression had metabolic asymmetries, most prominent in the posterio-inferior frontal area, which normalized with methylphenidate administration; these patients had a positive response to clinical tricyclic antidepressants. In a subsequent, larger series, Baxter et al. found that patients with unipolar depression had significantly lower metabolic ratios of caudate nucleus to whole hemisphere values than did two other patient groups or control subjects. Overall, these studies suggest a left anterolateral prefrontal cortex abnormality in major depression.

*Neurophysiology.* Concentration and attention are related to cortical arousal. An early measure of cortical arousal was the measurement of the threshold of barbiturate sedation. Both Hemsi et al. (80) and Cawley et al. (81) demonstrated sedation in elderly patients with depression at lower doses of barbiturate. The lower threshold for sedation was comparable to that in degenerative dementia. Electrophysiologic disturbances parallel these findings. For example, Hendrikson et al. (82) demonstrated latency delays in evoked auditory potentials in elderly depressed patients compared with age-matched control subjects. The delay was similar in direction but not as great as that in patients with primary degenerative dementia. The delayed response remained even after clinical improvement in depression. Brenner et al. (83) found that about one-third of waking EEGs from patients with primary degenerative dementia showed moderate to severe abnormalities, that patients with depressive dementia evidence a significantly higher percentage of generalized abnormal EEGs than do normal control subjects, and that patients with depressive pseudodementia show greater slowing of the dominant posterior rhythm than do normal control subjects. Overall, however, there is a large overlap between normal aging, major depression, depressive dementia and mild to moderate degenerative dementia.

More recent neurophysiological research has focused on sleep electroencephalography. The sleep EEG of the elderly person with depression but not dementia has been characterized by a shorter latency to the first REM period, a longer first REM sleep period, a higher percent of REM sleep, and greater density of phasic eye movements than the sleep of patients with primary degenerative dementia. In contrast, the sleep of subjects with degenerative dementia shows progressive loss of phasic eye movements during REM sleep, loss of spindles and K complexes in non-REM sleep, a tendency for the number of delta waves to decrease, and a tendency for slow-wave sleep to decrease (54, 84).

In comparing the sleep EEG profile of depressive dementia with that of primary degenerative dementia plus secondary depression, Buysse et al. (85) found a more predictable decrease in Hamilton Rating Scale for Depression scores following night-long sleep deprivation, a higher percent of REM sleep and greater phasic REM activity/intensity, and a longer first REM period on the second recovery night following sleep deprivation in patients with depressive dementia. The differences in REM sleep rebound permitted correct identification of 89% of the patients. Using a sophisticated statistical approach, Reynolds et al. (47) were able to classify 80% of patients with major depression or degenerative dementia from normal elderly subjects. However, in patients with a mixed picture of depression and dementia, discrimination dropped to 64%.

*Neurochemistry.* The most consistent neurochemical abnormality in primary degenerative dementia is region-specific deficits in the brain cholinergic system. This is particularly relevant because of the close relationship between memory functions and cholinergic transmitters. The most specific reduction is in the enzyme choline acetyltransferase. The reduction of this enzyme tends to parallel the distribution of the neuropathological changes in different brain regions; concentrations of choline acetyltransferase are lower in the temporal cortex and hippocampus. In addition, there is atrophy and loss of cholinergic cell bodies in the nucleus basalis of Meynert in the basal forebrain (86). The most profound cholinergic deficit is in early-onset Alzheimer's disease, and the least deficit is in multi-infarct dementia, Huntington's disease, Parkinson's disease, and depression. No reproducible biochemical changes have been found at postmortem in depression, and there have been essentially no postmortem neurochemical studies of depressive dementia.

The assumption that a single neurotransmitter deficit is responsible for the cognitive impairment of degenerative dementia is probably too simplistic. The same assumption is too simplistic for depression. Lower brain concentrations of norepinephrine, serotonin, and dopamine have been reported in patients with primary degenerative dementia (34, 87). Patients with depression have also been found to have reduced CSF concentrations of norepinephrine and serotonin (88). Somatostatin, a neuropeptide and putative neurotransmitter widely distributed in the CNS, is lower in several areas of the hippocampus and neocortex in primary degenerative dementia. Lower levels of somatostatin have also been reported in depression (89). Similarly, arginine vasopressin, a neurohypophysial peptide, is lower in the CSF of patients with primary degenerative dementia, unipolar depression, and Korsakoff's syndrome (90).

A related and extensively studied neuroendocrine measure is the dexamethasone suppression test. This test does not discriminate between age-matched patients with differing types of depression and dementia disorders. A number of studies have demonstrated a nonsuppression rate in nondepressed patients with primary degenerative dementia as high as that reported in major depression (71).

*Peripheral markers in platelets.* Because blood platelets are embryologically related to synaptic membranes they are thought to reflect the condition of the CNS. They also may prove to map to genes associated with Alzheimer's disease. To the extent that this is true, at least three different abnormalities of platelet membranes may have important associations with abnormalities in the brains of patients with depression and or degenerative dementia. Imipramine binding sites are associated with presynaptic serotonin reuptake, and elderly patients with depression appear to have fewer of these sites than do patients with degenerative dementia and control subjects (91). It is not known what the overlap might be in patients with depressive dementia. Platelet membrane fluidity, which can influence a variety of cell functions such as receptor activity, appears to be greater in patients with early-onset Alzheimer's disease than in age-matched control subjects or elderly depressed patients (44).

Platelet monoamine oxidase activity increases with aging, particularly in women. Alexopoulos et al. (19) suggested on the basis of a series of studies that platelet MAO activity is higher in patients with degenerative dementia with and without depression and in patients with depressive dementia than in nondemented depressed patients.

## DISCUSSION

The majority of the historical, clinical, neuropsychological, and neurobiological research reviewed suggests that the cognitive impairment seen in depressive disorder during late life is real, not pseudo or simulated. Methodological problems occurred in each type of research reviewed. Despite these problems, the consensus of the research taken together is fairly consistent. The neuropsychological literature suggests that depressive dementia is somewhat closer in both scores and pattern to primary degenerative dementia than to major depression without dementia. It is as if the common factor of dementia in depressive dementia and primary degenerative dementia has more weight than the common factor of depression in major depression with and without dementia. The consensus of the neurobiological research is that cognitive impairment of depression is associated with a variety of organic abnormalities. Again, findings in dementia of depression are more like findings in degenerative dementia than in normal aging or depression without dementia. These primarily cross-sectional studies make it clear that depressive dementia and primary degenerative dementia are not identical and they do not occur together at all points in the history of their disease course. What is at issue is if, how, and why these differing disorders sometimes evolve into a common phenotypic presentation.

It seems clear that we cannot easily extrapolate from major depression to depressive dementia in an attempt to define the cognitive impairments and phenomenology of the latter. In some patients, cognitive impairment is severe enough to meet four of five *DSM-III-R* criteria for dementia. The one criterion not met is the circular, exclusionary criterion "cannot be accounted for by any nonorganic mental disorder, e.g., major depression accounting for cognitive impairment." Such severe cognitive impairment may be "pseudo-degenerative dementia," but it is not pseudodementia. Some of the longitudinal data reviewed suggest that over time the severe cognitive impairment of depression may not even be "pseudo-degenerative dementia." Heuristically speaking, we would suggest there are a number of ways to arrive at the common endpoint of the phenotype of degenerative dementia. We suggest that depressive dementia involves a diathesis or vulnerability for this common final pathway or presentation.

There are other ways to interpret the longitudinal data on the poor prognosis of many depressed patients with severe cognitive impairment. It is possible that these patients would have developed primary degenerative dementia independently of any depressive disorder. It is also possible that these patients already were suffering from primary degenerative dementia in a latent form that became manifest under the stress of depression and then gradually became permanent over the years. The prevalence of poor prognosis found in several studies (11, 17) is higher than would be expected from the usual prevalence figures of severe dementia (22; *DSM-III-R*). Even if the high prevalence of Alzheimer's disease found in the East Boston study (25, 92) is used, the risk of poor prognosis in several studies is still greater than expected from simple co-occurrence. Given the lower rate of major depression in the elderly, the apparently greater long-term rate of dementia in major depression during late life is all the more striking.

These observations emphasize the common problem of confusing diagnosis, organicity, and prognosis. As Lipowski (93) pointed out before *DSM-III*, the diagnosis of organic is only pragmatic: "It helps to distinguish a class of disorders that are best managed if their occurrence is assigned to the primary dysfunction of the physical substrate of information processing. This distinction does not imply a clear cut dichotomy." If a dementia is in any degree reversible, it is not ipso facto a false dementia or pseudodementia. This is certainly true according to the operational philosophy of *DSM-III* and *DSM-III-R*. If a dementia is to any extent reversible at any point in its course, this does not mean it is devoid of an organic etiology. We suggest that the evidence reviewed here supports viewing the cognitive impairment of depression as a continuum intersecting an organic degenerative continuum with a corresponding continuum of reversibility-irreversibility. Accordingly, using the term "depressive pseudodementia" appears to be as inappropriate as equating the terms "psychosomatic" and "psychogenic." In many respects it would be useful to have a qualifying *DSM-IV* category for major depressive disorder to denote severe cognitive impairment, analogous to the qualifier of depression for primary degenerative dementia.

### *Clinical Implications*

There are several clinical implications of the continuum point of view. This viewpoint helps lower unrealistic expectations of psychiatrically curable dementia. The viewpoint discourages stereotypically equating the concepts of reversibility, treatment, and cure. Instead, it provides a rationale for more aggressive treatment of "excess disability" (94) in patients with any degree of dementia. The continuum perspective acts to discourage a dichotomous approach to treatment that considers some patients treatable and others not treatable. The perspective also militates against the segmentation of biological and psychological treatments. Most elderly patients with cognitive impairment from depression have clear depressive symptoms qualifying for major depression. It is on the basis of, for example, the presence of intrapsychic depressive symptoms and characteristic sleep disturbance rather than the claim or presence of cognitive impairment that somatic treatments are recommended. Otherwise, an empirical trial of antidepressants for all elderly patients with severe cognitive impairment could result in unnecessary or even dangerous side effects. Similarly, patients with primary degenerative dementia who have sufficient depressive symptoms should be treated. However, patients with primary degenerative dementia who also have major depression should not necessarily be treated with somatic therapy. In the only double-blind study we found of antidepressants in Alzheimer's disease with major depression, supportive psychosocial therapy was as effective as somatic therapy (95). This also underscores problems inherent in a dichotomous organic versus nonorganic view.

These treatment implications do not imply a nihilistic attitude toward depression or dementia. Rather, they are meant to emphasize the importance of obtaining a good history and conducting a thorough mental status examination (cognitive and affective) as the basis for a treatment plan to alleviate primary or secondary impairment from depressive symptoms. Reliance on good clinical skills should decrease emphasis on expensive ancillary technologies for the differential diagnosis of depressive dementia and primary degenerative dementia of the Alzheimer type. Some of these technologies (e.g., neuroimaging) are useful for diagnosis, detection, and treatment of vascular disease components, such as multi-infarct dementia. At this time, however, most ancillary technologies have their primary role in research. Of great importance for the spectrum approach to treatment is long-term follow-up. For early detection and alleviation of incipient depressive and dementing symptoms, all disorders along the depression-dementia spectrum need to be traced and treated longitudinally.

### *Research Implications*

Clinical information and longitudinal follow-up should also form the basis of future research. Neuropsychological testing, sleep electroencephalography, neuroimaging techniques, and biochemical and neuropathological investigations all have primary importance in research. Longitudinal cost-effectiveness studies using these techniques would also be of relatively more immediate clinical value. For example, what combination of clinical data best predicts which patients would benefit from which techniques? Results from such studies could provide greater empirical support for defining the appropriate diagnostic evaluation of patients and determining what these evaluations would cost.

When depressive dementia is viewed on a continuum with degenerative dementia, however, overlapping pathophysiological mechanisms rather than differential diagnoses become an important focus. If the co-occurrence of depression and dementia is not due to chance alone, there are at least three possible relationships to be systematically investigated. First, the co-occurrence could be due to an interaction and threshold effect. For example, given an underlying predisposition (e.g., genetic diathesis) to develop dementia (or depression), combined with the CNS insult from depression (or dementia), a threshold is reached for the expression of that predisposition (17, 26, 42).

One important approach for investigating this relationship would be to use the techniques of molecular biology to determine if the neuritic plaques and neurofibrillary tangles seen in the different prototypical conditions not only vary continuously but also are qualitatively identical (96, 97) in subjects and family members. Similarly, efforts should be made to compare regional brain differences in neurotransmitter concentrations in the different prototypical conditions.

Second, the abnormalities so far noted may represent damage from depression (or dementia) and its treatment rather than distal causal factors. An important implication of this possibility is that we must give greater attention to the accurate determination of the number and duration of depressive episodes and type of treatment (e.g., use and duration of anticholinergic antidepressants and their effect on acetylcholine synthesis) in patients with depressive dementia.

Third, both depression and dementia may include a common pathophysiology but do not lead to one another. For example, certain alterations in membrane structure and physiology may be necessary but not sufficient for both disorders. The research reviewed indicates a need for further investigation of functional as well as structural abnormalities in neural networks involving subcortical nuclei in both depression and dementia. In this regard, it would be valuable and pioneering to administer neuropsychological tests (which can suggest subcortical dysfunction) to patients with depressive dementia studied with PET as well as to administer mood measures to patients with degenerative dementia studied with PET.

Other research directions include studying similarities and differences in the long-term course of bipolar affective disorder compared with unipolar major depression in relation to the degenerative dementing axis. Future research should also study the longitudinal occurrence of neuropsychological and neurobiological abnormalities in more accurately determined early- versus late-onset depression.

In order to pursue these hypotheses and directions, future research should include the establishment of multidimensional clinical and biological measures over substantial 5–10-year follow-up periods. The use of continuous outcome measures (e.g., depression or cognitive scale scores) as well as categorical diagnoses is also indicated in order to cover the entire spectrum from successful aging (without the subtle and not so subtle effects of preventable medical conditions [98]) to aging with disabling depression and dementia.

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# The *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified: Clinical Characteristics and Relationship to Other Psychiatric Disorders

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*Objective: The authors reviewed available studies of* DSM-III-R *impulse control disorders not elsewhere classified in order to determine the relationship of these disorders to one another and to other psychiatric disorders. Method: The review focused on the demographic and clinical characteristics, phenomenology, family history, biology, and response to treatment of individuals with intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania. Analysis was restricted to reports which either indicated use of operational diagnostic criteria or provided descriptions of the impulsive behavior detailed enough that patients could be judged as probably meeting the* DSM-III-R *criteria. Results: Although different impulse control disorders have different sex ratios, all have similar ages at onset and courses. Studies on phenomenology, family history, and response to treatment suggest that intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania may be related to mood disorders, alcohol and psychoactive substance abuse, and anxiety disorders (especially obsessive-compulsive disorder). Biological studies indicate that intermittent explosive disorder and pyromania may share serotonergic abnormalities similar to those reported in mood disorders. Conclusions: The impulse control disorders not elsewhere classified appear to be related to one another and to mood, anxiety, and psychoactive substance use disorders. Thus, like major depression, obsessive-compulsive disorder, panic disorder, bulimia nervosa, and attention deficit hyperactivity disorder, they may represent forms of "affective spectrum disorder."*

(Am J Psychiatry 1992; 149:318–327)

Impulse control disorders are broadly defined as mental disorders characterized by irresistible impulses to perform harmful acts (1–4). In *DSM-III-R*, impulse control disorders are defined by three essential features: 1) failure to resist an impulse, drive, or temptation to perform some act that is harmful to the person or others, 2) an increasing sense of tension or arousal before committing the act, and 3) an experience of pleasure, gratification, or release at the time the act is committed. In addition, there may or may not be conscious resistance to the impulse, the act may be or may not be premeditated or planned, and immediately after the act there may or may not be genuine regret, self-reproach, or guilt (*DSM-III-R*, p. 321). Thus, the behaviors can be ego-syntonic and/or ego-dystonic.

Despite this elaborate definition, *DSM-III-R* does not have a formal category for impulse control disorders. Rather, it has a category termed "impulse control disorders not elsewhere classified," which includes intermittent explosive disorder, kleptomania, pathological gambling, pyromania, trichotillomania, and impulse control disorder not otherwise specified. Potential members of this latter residual category include repetitive self-mutilation (5), compulsive shopping ("oniomania") (6), compulsive sexual behavior (7), and compulsive facial picking (8). Also, alcohol and psychoactive substance use disorders and the paraphilias, although not described as impulse control disorders in

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**TABLE 1. Overview of *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified**

| Disorder and Studies | Description | Prevalence | M/F Ratio | Usual Time of Onset | Course |
|---|---|---|---|---|---|
| Intermittent explosive disorder (11, 15–21)[a] | Episodic aggressive outbursts | Rare? | M>F | Childhood, adolescence, or early adulthood | Episodic and chronic |
| Kleptomania (22, 23) | Impulsive or compulsive stealing | Rare? | F>M | Childhood, adolescence, or early adulthood | Episodic or chronic |
| Pathological gambling (24–34) | Compulsive or addictive gambling | 0.2%–3.3% | M>F | Adolescence or early adulthood | Episodic or chronic, occurs in "bouts" |
| Pyromania (20, 21, 35, 36)[b] | Repetitive failure to resist impulses to set fires | Rare? | M>F | Childhood, adolescence, or early adulthood | Episodic or chronic |
| Trichotillomania (37–44) | Compulsive hair pulling | Rare? | F>M | Childhood, adolescence, or early adulthood | Episodic or chronic |

[a] Most patients were described as having episodic behavioral dyscontrol, explosive rage, rage outbursts, or impulsive aggression. Although many had overt or subtle neurological abnormalities, some had no detectable neurological abnormalities and thus probably met the *DSM-III-R* criteria for intermittent explosive disorder.

[b] Most patients were described as being impulsive fire setters or impulsive arsonists; whether or not the patients experienced irresistible impulses to burn was not consistently documented.

*DSM-III-R,* are given as examples of such in the *DSM-III-R* section defining the impulse control disorders not elsewhere classified.

Despite their inclusion in the formal American diagnostic nomenclature since 1980 and a rich descriptive literature dating back to the late nineteenth century, the impulse control disorders as a group remain poorly studied. Except for alcohol and psychoactive substance abuse, little is known about them in terms of prevalence, demographic characteristics, course, associated psychopathology, family history, and response to treatment. Nor is it entirely clear why these individual conditions are grouped together. For example, while *DSM-III-R* characterizes impulse control disorders by the inability to resist "an impulse, drive, or temptation" to perform a harmful act, it does not explicitly require this criterion for intermittent explosive disorder, pathological gambling, pyromania, or the alcohol and psychoactive substance use disorders. Indeed, since nearly the inception of the concept of impulse control disorders, the validity of the so-called irresistible impulse has been questioned (9, 10), as has the diagnostic legitimacy of several specific impulse control disorders, including intermittent explosive disorder (3, 11), kleptomania (9, 12), and pyromania (9, 13, 14).

In an attempt to address some of these issues regarding *DSM-III-R* impulse control disorders not elsewhere classified, we surveyed the literature for studies of the epidemiology and phenomenology of these disorders and patients' associated psychopathology, family history, biology, and response to somatic and psychosocial treatments. We restricted analysis to reports which either indicated use of operational diagnostic criteria or provided descriptions of the impulsive behavior detailed enough that patients could be judged as probably meeting the *DSM-III-R* criteria. We omitted from analysis the paraphilias and alcohol and substance use disorders. Although given as examples of other impulse control disorders in *DSM-III-R* (p. 321), these disorders are presently assigned in *DSM-III-R* to separate diagnostic categories. Moreover, a detailed review of the paraphilias and alcohol and substance abuse, although needed, is beyond the scope of this article. We also omitted studies of behaviors meeting criteria for impulse control disorder not otherwise specified, because the number of patients studied (except for those with repetitive self-mutilation) was extremely small.

## PREVALENCE, COURSE, AND PATIENT CHARACTERISTICS

Information about the prevalence and course of the impulse control disorders not elsewhere classified and about patients' demographic and clinical characteristics is provided in table 1. All of these disorders, with the exception of pathological gambling (26, 34), are presumed to be rare (19, 22, 36, 37). Although certain *behaviors,* such as shoplifting, gambling, and fire setting, are common in the general population, studies have generally shown that only a small portion of such individuals perform the behavior in response to irresistible impulses and hence represent cases of true impulse control *disorders* (e.g., kleptomania, pathological gambling, and pyromania) (22, 25, 35, 36, 45, 46). Moreover, although many studies have examined large groups of individuals who display impulsive aggression (commonly called "episodic behavioral dyscontrol"), many of the individuals studied do not appear to have had intermittent explosive disorder according to *DSM-III-R* criteria, because the dyscontrol was attributed to a primary neurological or organic mental disorder (11, 15–18). Nevertheless, except for pathological gambling, the prevalences of these impulse control disorders in the general population have not been well studied, and some authors have speculated that certain impulse control disorders, such as episodic dyscontrol (17), kleptomania (22), and trichotillomania (40, 44), may be more common than realized.

Although these impulse control disorders have different sex ratios, they appear similar with respect to onset and course (see table 1). Most cases begin in adolescence or early adulthood (except for trichotillomania, a substantial number of cases of which begin in child-

**TABLE 2. Evidence From Phenomenologic Studies of Other Psychiatric Disorders in Patients With *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified**

| Disorder and Studies | Degree of Association With Impulse Control Disorder[a]<br>Mood Disorders | Anxiety Disorders | Alcohol or Substance Abuse | Eating Disorders | Attention Deficit Hyperactivity Disorder | Personality Disorders |
|---|---|---|---|---|---|---|
| Intermittent explosive disorder (11, 16–18, 20, 21, 47, 48) | 1 | 1 | 3 | —[b] | 2 | 2 |
| Kleptomania (22, 23, 49–54) | 3 | 3 | 3 | 3 | —[b] | 1 |
| Pathological gambling (25, 27, 28, 31–33, 55–57) | 4 | 3 | 4 | —[b] | 2 | 2 |
| Pyromania (20, 21, 36, 58, 59) | 2 | —[b] | 2 | —[b] | 1 | 1 |
| Trichotillomania (38, 41–44, 60–64) | 3 | 3 | 3 | 2 | —[b] | 1 |

[a] 4=Supported by two or more studies using structured interviews to diagnose patients by operational criteria, 3=supported by one study using structured interviews to diagnose patients by operational criteria, 2=supported by studies using nonoperational diagnostic criteria, 1=supported by case reports or small case series, 0=not supported by balance of evidence.

[b] Insufficient data.

hood [44]) and follow a chronic course with exacerbations and remissions. However, little is known about the evolution of these disorders with advanced age.

## ASSOCIATED PSYCHOPATHOLOGY

Studies examining the relationship between these five impulse control disorders and other psychiatric disorders are summarized in table 2. Operational diagnostic criteria have been used to systematically study phenomenology in four studies of intermittent explosive disorder (N=24) (20, 21), three of which used the same cohort of patients and were extensions of the first, in one study of kleptomania (N=20) (23), in five studies of pathological gambling (N=99) (27, 28, 31–33), three of which presumably used virtually the same cohort of patients, and in two studies of trichotillomania (N=76) (41, 42). Although none of these studies was controlled, all but one (20, 21) showed high rates of mood disorder, ranging from 43% among 14 trichotillomanic patients (41) to 100% among 20 kleptomanic patients (23). Of 99 pathological gamblers, 83 (84%) displayed mood disorder (28, 31, 33), and of 64 patients with trichotillomania, 46 (72%) had mood disorder (41, 42). In the only follow-up study located (32), of 38 pathological gamblers who were "abstinent" 6 months after inpatient treatment, seven (18%) were "still significantly depressed" despite improvement in work and family life.

Only one study compared the ages at onset of impulse control disorder and of mood disorder (23). Among 20 patients with concomitant kleptomania and mood disorder, the onset of mood disorder preceded the onset of kleptomania by at least 1 year in 12 (60%), occurred within the same year in three (15%), and occurred after the onset of kleptomania in five (25%). In a study of 25 pathological gamblers (31), 18 (72%) experienced episodes of major depression around the time that they first stopped gambling. Thirteen (52%) subjects experienced additional major episodes of mood disorders (major depression in 11 and mania in two) either before they stopped gambling or afterward. Of note, particularly high rates of bipolar disorders (types I and II and cyclothymia) were reported in patients with kleptomania (60%) (23) and in pathological gamblers (32% and 46%) (28, 31). Furthermore, some patients with kleptomania and pathological gambling reported relationships between their impulse control disorders and mood symptoms: their irresistible impulses would alter in intensity or frequency when they were depressed or manic, or their impulsive behaviors would affect their affective symptoms. In particular, patients reported that stealing or gambling produced a pleasurable "rush" that alleviated their depressive or manic symptoms (23, 28). Interestingly, some patients likened this "rush" to their hypomanic or manic episodes (23).

Phenomenologic studies also have shown high rates of concomitant anxiety (23, 31, 41, 42), alcohol and psychoactive substance abuse (20, 21, 23, 27, 28, 31, 33, 41, 42), and eating disorders (23, 42) in patients with these impulse control disorders. Specifically, of 24 impulsive offenders (20, 21), all met the *DSM-III-R* criteria for alcohol abuse. Of 20 patients with kleptomania (23), 16 (80%) each met the *DSM-III-R* criteria for at least one anxiety disorder (panic disorder, 40%; agoraphobia, 5%; social phobia, 40%; simple phobia, 30%; obsessive-compulsive disorder, 45%); 12 (60%) met the criteria for an eating disorder (bulimia nervosa, 60%; anorexia nervosa, 30%); and 10 (50%) met the criteria for a psychoactive substance use disorder (most commonly alcohol, amphetamine, and cocaine). Of 49 pathological gamblers from two studies (31, 33), 11 (22%) each had at least one anxiety disorder, most commonly obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and simple phobia. Of 100 pathological gamblers from three studies (27, 31, 33), 42 (42%) had histories of alcohol or substance abuse. Finally, of 74 patients with trichotillomania from two studies (41, 42), 39 (53%) had histories of anxiety disorders (including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder) and 17 (23%) had histories of alcohol or drug abuse.

These findings are further supported by numerous case reports and case series of individuals with apparent impulse control disorders who also had concurrent or past mood disorders (22, 25, 38, 44–56, 60–64), obsessive-compulsive disorder (22, 35, 43), panic disorder (22, 50), eating disorders (22, 38, 50, 54, 62), or alcohol or substance abuse (16, 18, 22, 54). Studies have also shown relatively high rates of impulsive stealing or kleptomania among patients with eating disorders (22, 65, 66) and high rates of pathological or problem gambling among alcoholics (67). For episodic dyscontrol and pathological gambling, studies further suggest a relationship with attention deficit hyperactivity disorder (11, 16, 57) and personality disorder (12, 20, 21, 32).

We were unable to locate any systematic studies of individuals with rigorously diagnosed pyromania. Although there have been many studies of large groups of individuals who displayed impulsive fire-setting behavior (20, 21, 35, 36, 46), most of the individuals studied either were not clearly identified as having pyromania (20, 21) or did not appear to have pyromania as defined by the *DSM-III-R* criteria (35, 36, 46). Nevertheless, these studies consistently showed high rates of concomitant alcohol and substance use disorders (20, 21, 35), personality disorders (20, 21, 46), and depression (20, 21, 46). For instance, in a study of 22 impulsive arsonists (20, 21), 15 (68%) of whom met the *DSM-III-R* criteria for intermittent explosive disorder, 21 (95%) also met the *DSM-III-R* criteria for dysthymic disorder (N=18) or major depression (N=3), 20 (91%) met the criteria for alcohol abuse, and 20 (91%) met the criteria for borderline (N=17) or antisocial (N=3) personality disorder. Further, cases of individuals with apparent pyromania and concomitant mood disorder or obsessive-compulsive disorder have been reported (35, 58, 59). Finally, individuals with episodic dyscontrol have been reported to display high rates of fire-setting behavior (16).

## FAMILY STUDIES

Family studies of individuals with impulse control disorders not elsewhere classified are less extensive than phenomenologic studies. However, the most consistent findings have been high rates of mood and substance use disorders in the first-degree relatives of individuals with intermittent explosive disorder or episodic dyscontrol (some of whom probably had intermittent explosive disorder) (16, 17, 20, 21, 68, 69), kleptomania (23), and pathological gambling (27, 31, 33). For instance, Mattes and Fink (68) reported that of 132 first-degree relatives of 33 patients with temper outbursts (22 of whom had intermittent explosive disorder), 11% had depression and 8% alcohol or drug abuse. Linnoila et al. (69) found that 44 (81%) of 54 violent offenders and impulsive fire setters (29 with intermittent explosive disorder) had first- or second-degree relatives with alcoholism. Among 103 first-degree relatives of 20 subjects with kleptomania (23), 22 (21%) had major mood disorder and 21 (20%) had alcohol or substance use disorders. Among 175 first-degree relatives of 25 pathological gamblers (31), 18 (10%) displayed major mood disorder and 19 (11%) displayed alcohol abuse or dependence. Similarly, Ramirez et al. (27) found that 50% of 51 patients with pathological gambling each had an alcoholic parent, and Roy et al. (33) reported that 33% and 25% of 24 pathological gamblers each had a first-degree relative with mood disorder and alcohol abuse, respectively.

Although not as striking, relatively high rates of anxiety disorders (in particular, panic disorder, agoraphobia, and obsessive-compulsive disorder) have been reported in families of individuals with kleptomania (23) and trichotillomania (44). Other findings include high rates of obsessive-compulsive personality disorder in families of individuals with trichotillomania (43), high rates of violence (16, 17, 68) and attention deficit hyperactivity disorder (68) in families of individuals with episodic dyscontrol, and possibly higher than normal rates of the same impulse control disorder in the families of patients with intermittent explosive disorder (6.9%) (68), kleptomania (2%) (23), pathological gambling (23%) (27), and trichotillomania (5%) (44, 64). Finally, Winokur et al. (70) noted an apparently high prevalence of pathological gambling in the families of bipolar probands.

## STUDIES OF BIOLOGICAL TESTS

Studies of biological tests of subjects with impulse control disorders not elsewhere classified, summarized in table 3, have largely focused on the hypothalamic-pituitary-adrenal axis, on serotonin, norepinephrine, and glucose metabolism, and on EEG results. For the most part, the subjects have been individuals with impulsive aggression, impulsive fire setting, and pathological gambling. The most consistent findings have been abnormalities in serotonergic and, to a lesser extent, noradrenergic function (74, 75). For instance, Brown et al. (72) reported that a higher degree of impulsivity correlated with a higher aggression score and lower CSF 5-hydroxyindoleacetic acid (5-HIAA) but higher 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations in 26 men with personality disorders. Of note, the 11 subjects with histories of at least one suicide attempt had higher aggression scores and lower 5-HIAA and higher MHPG concentrations than the subjects with no history of suicide attempts. In a study of 58 violent offenders and impulsive fire setters, 33 (57%) of whom met the *DSM-III-R* criteria for intermittent explosive disorder, Virkkunen et al. (20, 21) found lower CSF concentrations of 5-HIAA and MHPG in the impulsive offenders and fire setters than in the nonimpulsive offenders and normal comparison subjects. Moreover, low 5-HIAA and MHPG concentrations were associated with a lifetime history of suicide attempts. More recently, Brown et al. (76) reported that mean platelet $[^3H]$serotonin uptake was significantly lower in 15 male outpatients with episodic aggression than in 15 nonaggressive comparison subjects.

By contrast, individuals with pathological gambling

**TABLE 3. Biological Findings on Patients With *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified**

| | Relation of Biological Findings to Normal | | | |
|---|---|---|---|---|
| Disorder and Studies | Cortisol | 5-HT | Norepinephrine | Other[a] |
| Impulsive violent behavior (11, 16–18, 20, 21, 69, 71–76)[b] | No difference in urinary free cortisol | Lower CSF 5-HIAA; lower platelet 5-HIAA uptake | Lower CSF MHPG | Lower blood glucose on GTT;<br>EEG abnormalities |
| Pathological gambling (29, 33, 77, 78) | Suppression on DST | No difference in plasma 5-HIAA | Lower plasma and higher CSF MHPG[c]; higher urinary norepinephrine | Differential EEG activation |
| Impulsive fire setting (20, 21, 69, 73, 79) | No difference in urinary free cortisol | Lower CSF 5-HIAA | Lower CSF MHPG | Lower blood glucose on GTT |

[a] GTT=glucose tolerance test.

[b] Some, but not all, patients met the *DSM-III* criteria for intermittent explosive disorder.

[c] Only the centrally produced fraction of CSF MHPG was higher than normal. Total CSF MHPG was not higher than in comparison subjects.

**TABLE 4. Efficacy of Psychosocial Treatments for *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified**

| | Rating of Efficacy[a] | | | | |
|---|---|---|---|---|---|
| Disorder and Studies | Insight-Oriented Psychotherapy | Behavioral Therapy | Group Therapy | Inpatient Treatment | Self-Help Groups |
| Intermittent explosive disorder (16, 17, 80) | 1/0[b] | —[c] | 1 | —[c] | —[c] |
| Kleptomania (22, 23, 50, 53, 81) | 1 | 1 | —[c] | —[c] | —[c] |
| Pathological gambling (82–88) | 2/0[b] | 2 | —[c] | 2 | 1 |
| Pyromania | —[c] | —[c] | —[c] | —[c] | —[c] |
| Trichotillomania (39, 44, 89–91) | 1 | 3 | —[c] | —[c] | —[c] |

[a] 3=Supported by one controlled study, 2=supported by at least one open study, 1=supported by single case reports or small case series, 0=not supported by balance of evidence, but limited evidence for efficacy may be present.

[b] Ratings of evidence for positive and negative findings, respectively.

[c] Insufficient data.

have been shown to have significantly lower plasma MHPG concentrations, greater centrally produced fractions of CSF MHPG, and greater urinary output of norepinephrine than comparison subjects, but similar CSF 5-HIAA concentrations (33). One study (77), however, demonstrated that pathological gamblers show normal suppression on the dexamethasone suppression test. Finally, studies have shown high rates of EEG and other neurologic abnormalities in individuals with intermittent explosive disorder (11), episodic dyscontrol (16–18), and pathological gambling (78).

## RESPONSE TO TREATMENT

Studies of psychosocial treatments of impulse control disorders not elsewhere classified are summarized in table 4. We were able to find only two controlled studies of any form of psychosocial treatment for the five impulse control disorders analyzed. In the first (86), imaginal desensitization was more effective than aversive therapy in reducing the urge to gamble, gambling behavior, and anxiety in 20 compulsive gamblers—at both 1 month and 1 year after treatment. In the second (91), habit reversal was twice as effective as negative practice training in suppressing hair pulling in 34 patients with trichotillomania. Open studies of psychoanalytic psychotherapy, various forms of behavioral therapy, and inpatient treatment using relatively large numbers of pathological gamblers have shown varying degrees of success (24, 30, 32, 85, 88). In addition, isolated case reports and case series have shown psychoanalytic or insight-oriented psychotherapy and behavioral therapy to be effective for kleptomania (22, 50, 53, 81), pathological gambling (83–85), and trichotillomania (39, 44, 90, 91). Case reports and case series have also shown some success of various forms of psychotherapy and behavioral therapy for children with fire setting typically not due to pyromania (92). However, a number of authors have commented on the difficulties involved in treating some of these individuals (especially those with intermittent explosive disorder, pathological gambling, pyromania, and trichotillomania), citing patients' refusal to take responsibility for their behavior, lack of insight, denial, concomitant legal difficulties, and alcohol abuse (40, 44, 82).

Studies examining the response of these impulse control disorders to pharmacologic treatments are summarized in table 5. We located no placebo-controlled trials and only two controlled trials of pharmacologic agents for individuals with impulse control disorders not elsewhere classified diagnosed by means of operational criteria. In the first, Swedo et al. (41) found clomipramine to be more effective than desipramine in the treatment of 13 women with trichotillomania. In the second, Mattes (11) reported that carbamazepine and propranolol were equally effective in reducing rage outbursts in 80 patients with a variety of diagnoses, including intermittent explosive disorder (N=51) and attention deficit disorder, residual type (N=38). Of note, the diagnosis of intermittent explosive disorder was associated with preferential response to carbamazepine, whereas the diagnosis of attention deficit hyperactivity disorder was associated with preferential response to propranolol. Additionally, a number of case reports and case series have shown a variety of thymoleptic agents to be effective in treating four of the five impulse control disorders analyzed. These included carbamazepine, lithium, desipramine, and clomipramine for apparent intermittent explosive disorder (47, 48, 93); amitriptyline, imipramine, nortriptyline, trazodone, fluoxetine, lithium, and valproate for kleptomania (22, 23, 51, 52, 54); lithium for pathological gambling (56); and imipramine, desipramine, clomipramine, isocarboxazid, fluoxetine, and lithium for trichotillomania (41, 43, 44, 60, 61, 63, 64). Also, individuals with kleptomania have been reported to respond to ECT (52). In most cases, the patients reported reductions in the frequency and intensity of their irresistible impulses and impulsive behaviors, usually after several weeks of treatment with doses of medication typically effective for mood disorder. In some instances, the irresistible impulses recurred after discontinuation of the medication and remitted again when the medication was reinstituted (52, 54). Finally, numerous case reports and open studies of individuals with impulsive aggression due to a variety of conditions (i.e., organic mental disorder, personality disorder, schizophrenia) showed amelioration of aggressive behavior in response to β blockers, carbamazepine and other antiepileptics, lithium, psychostimulants, antidepressants, and various hormonal manipulations (in particular, antiandrogen treatments) (15, 17, 93).

**TABLE 5. Efficacy of Pharmacological Treatments for *DSM-III-R* Impulse Control Disorders Not Elsewhere Classified**

| | Rating of Efficacy[a] | | |
|---|---|---|---|
| Disorder and Studies | Antidepressants | Lithium | Anticonvulants |
| Intermittent explosive disorder (11, 47, 48, 93)[b] | 1 | 1 | 3 |
| Kleptomania (22, 23, 51, 52, 54) | 2 | 1 | 1 |
| Pathological gambling (56) | —[c] | 1 | —[c] |
| Pyromania | —[c] | —[c] | —[c] |
| Trichotillomania (41, 43, 44, 60, 61, 63, 64) | 3 | 1 | —[c] |

[a] 3=Supported by one controlled study, 2=supported by at least one open study, 1=supported by single case reports or small case series, 0=not supported by balance of evidence, but limited evidence for efficacy may be present.

[b] Many patients, but not all, had neurological abnormalities.

[c] Insufficient data.

## DISCUSSION

Although long recognized, the impulse control disorders in general remain a mysterious group of conditions. Even their diagnostic validity, individually and as a category, remains in question. Authors doubting the legitimacy of these disorders have generally argued that afflicted individuals do not really experience "irresistible" impulses but, rather, have voluntary control over their impulsive behaviors, or that their impulsive behaviors are nonspecific symptoms secondary to other underlying psychiatric disorders. Nevertheless, the literature contains numerous descriptions, from different countries and different historical periods, of individuals who perform harmful behaviors in response to overpowering, uncontrollable, irresistible, or "morbid" impulses. These reports date back to the early nineteenth century, when Esquirol (94) introduced the term *monomanies instinctives* (instinctive monomanias) to describe a form of insanity characterized by performance of impulsive acts without motive, in response to "instinctive" or involuntary, irresistible impulses. Subsequent writers (14, 35) have described similar syndromes with terms such as "partial moral mania," "impulsive insanity," "psychopathic forms of reaction," or "impulse neuroses." Thus, the consistency of the description of the irresistible or morbid impulse makes it difficult to dismiss its validity as a specific psychiatric symptom. That the *DSM-III-R* impulse control disorders not elsewhere classified appear to share a similar core disturbance of impulsivity and compulsivity (the so-called "irresistible" or "morbid" impulse)—regardless of the behavior performed—further suggests that they are related and should be grouped together.

The available studies of these impulse control disorders also suggest that they may be etiologically related to a variety of other psychiatric or medical disorders, including obsessive-compulsive disorder, addictive disorders, mood disorders, impulse control disorders in general, and organic mental disorders. First, morbid impulses and their consequent acts resemble obsessions and compulsions. Thus, kleptomania, pathological gambling, pyromania, and trichotillomania have been hypothesized to be forms of obsessive-compulsive disorder (22, 35, 41, 44, 95). This conceptualization is supported by studies showing high rates of obsessive-compulsive disorder in individuals with kleptomania (22, 23), pathological gambling (31), and trichotillomania (41, 42), studies showing higher than normal rates of obsessive-compulsive disorder in the families of individuals with kleptomania (23) and trichotillomania (44), and the finding that clomipramine may be more effective than desipramine in the treatment of trichotillomania (41).

Second, others (52, 88) have postulated that certain impulse control disorders (especially kleptomania and pathological gambling) would be better conceived as addictive disorders. For instance, the irresistible impulse to steal or gamble resembles the urge to drink or use drugs, and the "high" sometimes experienced with stealing or gambling is similar to that induced by alcohol or drugs (22, 53, 96). Indeed, gambling has been described as inducing "a stimulating, tranquilizing, or pain-relieving response" (29), and "self-medication" of benzodiazepine withdrawal symptoms through the thrill of kleptomanic stealing has been reported (52). Further, pathological gamblers may develop tolerance (96) and physiological withdrawal symptoms—including tremulousness, headaches, abdominal pain, diarrhea, nightmares, and cold sweats—after abrupt discontinuation of gambling (97). Also, as reviewed in this paper, high rates of alcohol and substance abuse are seen among individuals with intermittent explosive disorder, episodic dyscontrol, kleptomania, pathological gambling, and impulsive fire setting, and high rates of pathological or problem gambling occur among individuals with alcohol or substance abuse (67). Finally, self-help groups based on Alcoholics Anonymous (e.g., Gamblers Anonymous) have been reported to be helpful in the treatment of some pathological gamblers (87).

Third, given the frequent occurrence of affective symptoms or mood disorders in individuals with each of the five impulse control disorders analyzed, the apparent relief of depressive symptoms in response to kleptomanic stealing and pathological gambling, and the response of intermittent explosive disorder, kleptomania, pathological gambling, and trichotillomania to treatment with thymoleptics, others have speculated that these impulse control disorders may be related to mood disorder (21–23, 28, 31, 47, 49, 51, 53).

Fourth, some authors have noted the phenomenologic similarities of alcohol and drug abuse, paraphilias, and bulimia nervosa to the *DSM-III-R* impulse control disorders not elsewhere classified (3). This observation plus the high rates of *other* impulsive behaviors in persons with these disorders have prompted some authors to suggest that *all* of these conditions should be viewed as sharing a fundamental problem in impulse control and thus should be classified as impulse control disorders. The impulsive behavior is seen either as a failure of self-soothing mechanisms or as an attempt to relieve a variety of uncomfortable symptoms (4, 5). Lacey and Evans (4), for instance, reported that a substantial number of patients with substance use disorders, eating disorders, "classic" impulse control disorders, self-harm, and personality disorders were characterized not just by the presenting symptoms but by multiple impulsive behaviors. They termed these individuals "impulsivists" and suggested that they had "multi-impulsive personality disorder." Indeed, cases of individuals displaying more than one "classic" impulse control disorder have been reported (23).

Finally, some authors (22) have postulated that impulse control disorders (especially intermittent explosive disorder, kleptomania, and pyromania) are caused by organic conditions that induce or increase impulsivity; such conditions include hypoglycemia, narcolepsy, head trauma, dementia, and epilepsy. The evidence supporting a relationship between the impulse control disorders and epilepsy, for instance, includes phenomenologic similarities between impulse control disorders and complex partial seizures (15, 17, 22) and reports of patients with intermittent explosive disorder and kleptomania who responded to treatment with antiepileptic agents (15, 17, 23).

None of these conceptualizations, however, seems sufficiently inclusive. The impulse control disorders not elsewhere classified share high comorbidity and other features not only with obsessive-compulsive disorder, alcohol and other substance use disorders, mood disorders, and eating disorders but also with anxiety disorders. What could account for this large overlap in features among these various disorders? In an earlier report (98), we summarized data suggesting that major depression and a group of seven other disorders—including obsessive-compulsive disorder, bulimia nervosa, panic disorder, and attention deficit hyperactivity disorder—represented a family of disorders sharing a possible common physiologic abnormality. We termed this hypothesized family "affective spectrum disorder." The apparent phenomenologic similarities of the impulse control disorders not elsewhere specified to obsessive-compulsive disorder and bulimia nervosa—both forms of affective spectrum disorder—together with evidence linking these impulse control disorders to several other forms of affective spectrum disorder (including panic disorder, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and major depression) might be parsimoniously explained by the hypothesis that the impulse control disorders not elsewhere classified themselves are also forms of affective spectrum disorder. Note that this hypothesis does *not* argue that the impulse control disorders are caused by affective spectrum disorder but, rather, that they may share the same postulated underlying physiologic abnormality as the other forms of affective spectrum disorder.

This hypothesis derives support from many of the major findings reviewed in this paper. These include 1) high rates of mood disorders (as well as anxiety and eating disorders) among individuals with kleptomania, pathological gambling, trichotillomania, and behavioral dyscontrol and among members of their families, 2) findings of serotonin and norepinephrine abnormalities in episodic dyscontrol and impulsive fire setting similar to those occurring in depression (99, 100), and 3) the response of a variety of these impulse control disorders to thymoleptics. Viewing the impulse control disorders not elsewhere classified as forms of affective spectrum disorder would also account for a number of other individual or anecdotal observations noted in this paper. These include case reports describing individuals with concurrent pyromania and major mood disorder (58, 59), findings of high rates of attention deficit hyperactivity disorder among pathological gamblers and individuals with behavioral dyscontrol (16, 17, 57), and findings of EEG abnormalities in pathological gamblers similar to those in individuals with attention deficit hyperactivity disorder (78). Additionally, among patients with bulimia nervosa, stealing has been associated with greater degrees of depression and obsessive-compulsive behavior (65). Also, many patients with other impulse control disorders (e.g., compulsive shopping, compulsive facial picking, and paraphilias) have been reported to have concurrent mood disorders and to respond to thymoleptics (6, 8). Indeed, the link of impulse control disorders to alcohol abuse (given as an example of an impulse control disorder in *DSM-III-R*) could be explained in part by the high rates of mood disorders found among alcoholics (101).

The hypothesis that impulse control disorders are forms of affective spectrum disorder is, of course, affected by several methodological limitations. Most important is the lack of systematic, controlled studies of impulse control disorders using operational diagnostic criteria. For instance, we were unable to locate any controlled phenomenologic or family history studies and only two controlled drug treatment trials.

Second, it might be argued that impulsive acts are not disorders in themselves but are merely nonspecific behaviors exhibited with greater than normal frequency in patients with mood disorders. These behaviors decline with thymoleptic treatment because the underlying, or primary, mood disturbance is corrected. This argument, however, fails to account for the observation that some patients experience irresistible impulses in the absence of affective symptoms and that most patients with mood disorders do not demonstrate irresistible impulses to perform harmful behaviors.

A third criticism is that the affective spectrum disorder hypothesis does not directly explain 1) the phenomenologic similarity of these impulse control disorders to complex partial seizures and the apparently high rates of epilepsy, EEG abnormalities, and other neurologic abnormalities among individuals with episodic dyscontrol, 2) the experience of withdrawal symptoms when the impulsive behavior is abruptly discontinued, 3) case reports and clinicians' impressions that some impulse control disorders may be associated with personality disorder, and 4) the response of behavioral dyscontrol to nonthymoleptic agents, in particular, β blockers.

Nevertheless, these criticisms aside, several lines of evidence suggest that the *DSM-III-R* impulse control disorders not elsewhere classified, or, more generally, disorders characterized by irresistible impulses or urges to perform specific senseless or harmful behaviors, may share a biological abnormality with other forms of affective spectrum disorder. The nature of this biological abnormality is unknown. However, accumulating findings from animal and human studies have implicated central serotonergic transmission in the regulation of sleep, appetite, sexual activity, and mood (behaviors typically deranged in mood disorder) (99); in the genesis of major depression and mania (99), suicide (74), obsessive-compulsive disorder (102), bulimia nervosa (103), panic disorder (104), and alcoholism (105); and in the expression of impulsive behavior (74, 75). Animal studies, for instance, demonstrate that serotonin deficit states are important in the expression of impulsive aggression (74, 75). Low CSF 5-HIAA concentrations similar to those found in impulsive arsonists and impulsive violent offenders have been found in individuals who have attempted or completed suicide (especially violent suicide) and homicide (74) and in patients with mood disorder (99). Taken together, these lines of evidence suggest that impulse control disorders, like other forms of affective spectrum disorder, may share an abnormality in serotonergic transmission.

However, it does *not* follow from this hypothesis that all forms of impulsivity or compulsivity are linked to one another or to mood disorder. Impulsive and compulsive behaviors are evident in a variety of psychiatric and neurologic conditions, including mood disorders, personality disorders, schizophrenia, Tourette's disorder, and epilepsy, as well as in normal mental life. Thus, various impulsive and compulsive behaviors most likely have different forms and etiologies. At this point, it appears only that "classic" impulse control disorders—disorders marked by irresistible, involuntary, and specific impulses or urges to perform harmful or senseless acts—may be forms of affective spectrum disorder.

In summary, despite a rich descriptive literature dating back over 150 years and their inclusion in the formal American psychiatric nomenclature since 1980, the impulse control disorders not elsewhere classified remain little studied. Debate over their diagnostic validity lingers, but many have argued that these and other impulse control disorders are legitimate mental disorders causing significant morbidity and that they are more common than realized. Substantial preliminary evidence, reviewed in this paper, suggests that intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania are, in fact, valid diagnostic entities; that they are related to one another and should be grouped together; and that they are related to mood disorder and other forms of affective spectrum disorder. Systematic, controlled studies using operational diagnostic criteria should be done to clarify the validity and nature of this relationship and to determine the relationship of these disorders to other impulse control disorders.

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# Dissociation and Posttraumatic Stress Disorder in Vietnam Combat Veterans

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*Objective: This study compared current dissociative symptoms and dissociation at the time of specific traumatic events in Vietnam combat veterans with posttraumatic stress disorder (PTSD) and Vietnam combat veterans without PTSD. Method: Vietnam combat veterans who sought treatment for PTSD (N=53) were compared to Vietnam combat veterans without PTSD (N=32) who sought treatment for medical problems. Dissociative symptoms were evaluated with the Dissociative Experiences Scale. Dissociation at the time of a combat-related traumatic event was evaluated retrospectively with the modified Dissociative Experiences Questionnaire. The Combat Exposure Scale was used to measure level of combat exposure. Results: There was a significantly higher level of dissociative symptoms, as measured by the Dissociative Experiences Scale, in patients with PTSD (mean=27.0, SD=18.0) than in patients without PTSD (mean=13.7, SD=16.0). This difference persisted when the difference in level of combat exposure was controlled with analysis of covariance. PTSD patients also reported more dissociative symptoms at the time of combat trauma, as measured retrospectively by the Dissociative Experiences Questionnaire (mean=11.5, SD=1.6) than non-PTSD patients (mean=1.8, SD=2.1). Conclusions: Dissociative symptoms are an important element of the long-term psychopathological response to trauma.*

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A relationship between dissociation and symptoms of posttraumatic stress has been hypothesized since the time of Pierre Janet (1–4). Janet coined the term dissociation as the opposite of association—literally, the lack of connection between one piece of memory or consciousness and another (1). According to his theory, susceptible individuals who respond to traumatic events with dissociation develop long-term changes in neurobiological systems. These result in dissociative responses to subsequent stressful events, increased general dissociative symptoms, and an increased risk for stress-related psychiatric disorders such as what is known today as posttraumatic stress disorder (PTSD) (5).

There have been isolated reports of dissociative symptoms in veterans of World War I, World War II, and the Vietnam war (6–15). In addition, a study conducted by Spiegel et al. found a significantly higher rate of hypnotizability in Vietnam veterans with PTSD than in other patient groups or in normal control subjects (16). Spiegel et al. concluded that Vietnam veterans with PTSD may have more dissociative symptoms than other veterans.

The recent development of standardized instruments has made the measurement of dissociative symptoms possible. However, only one study has been published in which dissociative symptoms were measured in Vietnam veterans with PTSD (17). In that study, patients

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with PTSD had levels of dissociative symptoms that were higher than those of patients with temporal lobe epilepsy and comparable to those of patients with multiple personality disorder (17). There have been no published reports thus far comparing patients with PTSD to a control group of combat veterans without PTSD. If Janet's theory is correct, certain susceptible individuals—those who develop PTSD—would be more likely to develop dissociative symptoms than other less susceptible individuals.

This study was undertaken, therefore, to determine if there are higher levels of dissociative symptoms, both currently and at the time of traumatic events, in combat veterans with PTSD than in combat veterans without PTSD. An effort was also made to determine whether dissociation is specific to PTSD symptoms or whether it is associated with nonspecific psychiatric distress.

## METHOD

The subjects were 85 Vietnam combat veterans at the West Haven Veterans Administration (VA) Medical Center. The Vietnam combat veterans with PTSD (N=53) had sought treatment for PTSD and included patients consecutively admitted to the inpatient unit (N=34) of the National Center for Post-Traumatic Stress Disorder, Division of Clinical Neurosciences, West Haven VA Medical Center, during a 5-month period. Patients with PTSD were also from the outpatient clinic of the national center (N=19) and were selected from patients consecutively admitted during a 3-month period by clinicians who were willing to refer their patients to be interviewed. Vietnam combat veterans without PTSD (N=32) had sought treatment for medical problems and were patients consecutively admitted to the medical center's outpatient ambulatory care clinic during a 3-month period.

Patients included in the study were those with a history of combat exposure, defined as having received hostile or friendly fire or having received incoming artillery rounds. Patients were assigned to PTSD and non-PTSD groups on the basis of a diagnosis of current PTSD as measured by the Structured Clinical Interview for DSM-III (SCID) (18). Patients with a history of psychosis, organic brain syndrome, or a medical illness that would preclude participation were excluded from the study. Of the 89 Vietnam combat veterans contacted, 85 (97.4%) agreed to participate in the study.

Dissociative symptoms were evaluated with the Dissociative Experiences Scale (19). The scale is a 28-item, self-report instrument for the measurement of dissociative experiences; it has a test-retest reliability of 0.84 (20). The scale has been used in large population samples and has been shown to discriminate significantly between patients with dissociative disorders or other disorders and normal control subjects when a cutoff score of 30 is used (19–21). The scale is intended for use in screening for dissociative symptoms and is not a diagnostic instrument.

Higher levels of combat exposure were anticipated in the PTSD patient group than in the non-PTSD patient group. Level of combat exposure was assessed with the Combat Exposure Scale, a self-report measure that has been shown to have acceptable reliability and validity (22). High combat exposure is defined as a score of greater than 24 on the scale (T.M. Keane, personal communication, Oct. 15, 1990).

An additional component of the study involved a comparison of dissociative symptoms to PTSD symptoms and general psychiatric symptoms. For this purpose, patients were evaluated with the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder, a validated measurement of current PTSD symptom severity (23). The Mississippi scale assesses the full range of PTSD symptoms and quantifies scope and severity of symptoms. General psychiatric symptoms were examined with the global scale of the Brief Symptom Inventory. The inventory is a validated self-report instrument that assesses a broad range of psychiatric symptoms (24).

Dissociation at the time of traumatic events was examined with the modified Dissociative Experiences Questionnaire, which was developed for the purposes of this study. The questionnaire is a clinician-administered instrument for the assessment of dissociative states at specific time points; it consists of six questions from the Dissociative Experiences Questionnaire (C. Marmar, unpublished) and seven questions from another dissociation scale in development at our center (J.D. Bremner et al., unpublished). The questionnaire assesses the areas of amnesia, depersonalization, and derealization. Score is determined by the total number of positive responses to the 13 questions about dissociative states. Patients were asked to relate their most traumatic combat-related event, and the questionnaire was used in the assessment of dissociative states at that time. Specifically, symptoms in the areas of amnesia, depersonalization, and derealization were assessed.

Data from the Dissociative Experiences Scale were analyzed with standard parametric statistical methods. Since we anticipated a higher level of combat exposure in the PTSD group than in the non-PTSD group, we used analysis of covariance to compare scores on the Dissociative Experiences Scale for the PTSD and non-PTSD groups while controlling for the difference in combat exposure. To assess the relationship between dissociation (Dissociative Experiences Scale), PTSD symptoms (Mississippi scale), and nonspecific psychiatric symptoms (Brief Symptom Inventory global score), bivariate correlations were performed between scores on the Mississippi scale, Dissociative Experiences Scale, and the Brief Symptom Inventory-global scale in a subgroup of 40 PTSD patients. In order to assess the relationship between PTSD symptoms and dissociative symptoms while controlling for nonspecific psychiatric symptoms, we performed multiple linear regression in this subgroup. Multiple linear regression was also used to assess the relationship between dissociation at the time of combat trauma (modified Dissociative Experiences Questionnaire) and current PTSD symptom se-

**TABLE 1. Characteristics of Vietnam Combat Veterans With and Without PTSD Who Were Evaluated for Dissociative Symptoms**

| | PTSD Subjects (N=53) | | | | Comparison Subjects (N=32) | | | |
|---|---|---|---|---|---|---|---|---|
| Item | N | % | Mean | SD | N | % | Mean | SD |
| Age (years) | | | 42.4 | 2.7 | | | 43.0 | 2.2 |
| Race/ethnicity | | | | | | | | |
| Black | 8 | 15 | | | 4 | 13 | | |
| Hispanic | 1 | 2 | | | 2 | 6 | | |
| White | 44 | 83 | | | 26 | 81 | | |
| Education (years) | | | 12.9 | 1.8 | | | 12.9 | 1.9 |
| Marital status | | | | | | | | |
| Married | 23 | 43 | | | 11 | 34 | | |
| Separated | 4 | 8 | | | 1 | 3 | | |
| Divorced | 17 | 32 | | | 9 | 28 | | |
| Never married | 9 | 17 | | | 11 | 34 | | |
| Service branch | | | | | | | | |
| Army | 29 | 55 | | | 22 | 69 | | |
| Navy | 2 | 4 | | | 2 | 6 | | |
| Air Force | 3 | 6 | | | 1 | 3 | | |
| Marines | 19 | 36 | | | 7 | 22 | | |
| Age at time of joining the military (years) | | | 18.3 | 1.2 | | | 18.5 | 1.2 |
| Time in Vietnam (months) | | | 15.8 | 5.9 | | | 14.1 | 9.0 |

**TABLE 2. Psychological Scale Scores and Number of Flashbacks for Vietnam Combat Veterans With and Without PTSD**

| | PTSD Subjects (N=53) | | Comparison Subjects (N=32) | |
|---|---|---|---|---|
| Item | Mean | SD | Mean | SD |
| Dissociative Experiences Scale score | 27.0 | 18.0 | 13.7[a] | 16.0 |
| Mississippi Scale score | 130.2 | 16.0 | 82.5[a] | 21.1 |
| Combat Exposure Scale score | 32.0 | 6.2 | 20.8[a] | 9.8 |
| Brief Symptom Inventory global score | 2.24 | 0.73 | 0.92[a] | 0.75 |
| Number of flashbacks since Vietnam | 15.76 | 7.81 | 0.73[a] | 3.48 |

[a] p<0.01.

verity (Mississippi Scale for Posttraumatic Stress Disorder) in a subgroup of 51 patients with and without PTSD. Covariates adjusted for in the model were other combat-related variables including combat exposure, exposure to atrocities, and number of months spent in Vietnam. Two-tailed tests of significance were used in all the analyses, and significance was defined as p<0.05.

## RESULTS

There were no significant differences in any of the demographic variables measured between combat veterans with and without PTSD (table 1).

Scores of the PTSD patients on the Dissociative Experiences Scale were almost double those of the non-PTSD patients: 27.0 versus 13.7 (table 2). Scores greater than 30 were present in 41.0% of patients with PTSD, compared with 10.7% of non-PTSD patients ($\chi^2$=7.37, df=1, p<0.01).

Combat exposure, as measured by the Combat Exposure Scale, was significantly greater in the PTSD patients than in the non-PTSD patients (table 2). However, a significant difference in Dissociative Experiences Scale scores between the PTSD and non-PTSD groups persisted when the difference in combat exposure between the groups was controlled for with analysis of covariance (F=12.29, df=2, 59, p<0.05).

PTSD patients had higher levels of nonspecific psychiatric distress, as measured by the Brief Symptom Inventory (table 2). The relationship among dissociative symptoms, PTSD symptoms, and nonspecific psychiatric symptoms was examined in a subgroup of Vietnam combat veterans with PTSD. Bivariate analysis showed a correlation between dissociative symptoms (Dissociative Experiences Scale) and PTSD symptoms (Mississippi scale) (r=0.34, df=39, p=0.03), as well as between dissociative symptoms and nonspecific psychiatric symptoms (r=0.47, df=39, p=0.002). When the relationship between dissociative symptoms and PTSD symptoms was examined while nonspecific psychiatric symptoms were controlled for in the PTSD patients by using multiple linear regression, scores on the Mississippi scale were more strongly associated with scores on the Brief Symptom Inventory (beta=0.75, df=1, 37, p<0.05) than with scores on the Dissociative Experiences Scale (beta=0.02, df=1, 37, p=0.90).

A significant difference was also observed between the PTSD and non-PTSD groups in the level of dissociation at the time of combat-related traumatic events. Scores on the modified Dissociative Experiences Questionnaire were significantly higher in the PTSD group than in the non-PTSD group (mean=11.5, SD=1.6 versus mean=1.8, SD=2.1) (t=20.58, df=60, p<0.001). Dissociation at the time of combat trauma in a subgroup of patients with and without PTSD was associated with current PTSD symptom severity (measured by the Mississippi scale), determined by multiple linear regression. Covariates adjusted for in the model included level of combat exposure, participation in atrocities, and number of months in Vietnam. Dissociation at the time of the combat trauma showed the strongest association (beta=0.53, df=1, 45, p=0.0001); of the other variables included in the model, only participation in atrocities showed a significant association (beta=0.26, df=1, 45, p=0.02).

## DISCUSSION

In this study of Vietnam veterans there was a significantly higher level of dissociative symptoms in combat veterans with PTSD than in combat veterans without PTSD. The higher level of dissociative symptoms associated with PTSD persisted after the difference in combat exposure between the PTSD and non-PTSD groups was controlled for. In addition, level of dissociative symptoms was correlated with severity of PTSD symptoms as measured by the Mississippi scale.

These findings suggest that dissociation is associated with PTSD and that combat exposure alone does not explain the high levels of dissociative symptoms seen in veterans with PTSD. Certain individuals may be more susceptible than others to develop dissociative symptoms in response to the stress of combat. This may provide support for Janet's theory that susceptible individuals who respond to traumatic events with dissociation are at a higher risk of developing trauma-related psychiatric disorders such as PTSD.

The high rate of dissociative symptoms in patients with PTSD is consistent with other studies (17, 22, 25). PTSD patients' scores on the Dissociative Experiences Scale (mean=27.0, SD=18.0) were similar to those of a previously reported sample of Vietnam veterans with PTSD (mean=27.5) (17) and were higher than scores of a group of men between the ages of 41 and 50 who were selected from a general population sample (mean=8.7, SD=9.3) (28). Scores on the Dissociative Experiences Scale showed a wide range, as evidenced in the high standard deviations in both the PTSD and non-PTSD groups. It appears that there are subgroups of PTSD patients with high dissociative symptoms and other subgroups with low dissociative symptoms. In fact, inspection of individual Dissociative Experiences Scale scores in the PTSD patient group suggested that this was the case. There may be factors unrelated to combat that influence the level of dissociative symptoms in patients with combat-related PTSD. In addition, the non-PTSD patients in our study had higher scores on the Dissociative Experiences Scale (mean=13.7, SD=16.0) than men of the same age group from the general population sample. The wide range in scale scores in the non-PTSD group may be explained by the fact that there were some veterans in the non-PTSD group who suffered from partial PTSD. These veterans may have high levels of dissociative symptoms when compared to a cross-section of the general population, although not to the degree of patients who meet full criteria for PTSD.

Our findings also suggest a connection between dissociation at the time of combat trauma and the development of PTSD. There was a significant difference in dissociative response at the time of traumatic combat-related events between PTSD and non-PTSD patients, although the results should be interpreted with caution because of retrospective reporting. PTSD patients frequently reported experiences of amnesia at the time of traumatic events, such as one veteran who said, "After I saw my buddy hit, something inside of me died, and I don't remember anything that happened after that." Veterans also reported experiences of derealization, such as, "Everything seemed to be in slow motion," "Colors were blurred," "There was no sound," and "It seemed as if I were in a tunnel." Similarly, depersonalization was reported, as in the case of another veteran who said, "I felt myself separating from myself and looking down at the person who was in combat, and feeling sorry for him." Our findings are consistent with the literature, which suggests an association between trauma and dissociation (26–34).

What distinguishes individuals who are prone to dissociation at the time of combat trauma? One possibility is that discrete traumatic events may have a variable impact depending on the individual. PTSD patients in our study frequently reported dissociation after events that had personal significance for them, such as witnessing the death of a close friend. Another possibility is that degree of hypnotizability predisposes individuals to dissociation. Degree of hypnotizability has been associated with level of dissociative symptoms (35), and patients with PTSD have been found to have a higher degree of hypnotizability than other patient groups (16, 25). Variations in hypnotizability have been noted in the general population (36); these variations are stable over time (37). There is also some evidence which suggests that hypnotizability may have a genetic basis (38). Hypnosis has been advocated as a therapeutic treatment for posttraumatic stress disorder (39). Perhaps highly hypnotizable individuals are more likely to dissociate at the time of trauma and hence to develop trauma-related psychopathology.

It is important to note that dissociative symptoms do not appear to be uniquely associated with PTSD symptoms. Scores on the Mississippi scale were more strongly associated with scores on the Brief Symptom Inventory-global scale than with scores on the Dissociative Experiences Scale. It is possible that dissociation is associated with the higher level of nonspecific psychiatric symptoms seen in patients with PTSD and not with PTSD-specific symptoms that are measured by the Mississippi scale. Such conclusions should be made with caution, however, since the relationship between nonspecific psychiatric symptoms and specific PTSD symptoms in patients with PTSD is still under investigation. Future studies of combat veterans with psychiatric disorders other than PTSD are required in order to determine whether higher levels of dissociative symptoms are specific to PTSD.

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# Exposure to Atrocities and Severity of Chronic Posttraumatic Stress Disorder in Vietnam Combat Veterans

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*Objective: The authors' objective was to explore aspects of trauma associated with severity of posttraumatic stress disorder (PTSD) in Vietnam veterans. Method: Several ratings of stress exposure and symptom severity were administered to 40 patients with combat-related PTSD. Results: A significant relationship was observed between exposure to atrocities and the impact of PTSD on veterans' lives, as measured by the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder. Exposure to atrocities was also significantly correlated with current symptom severity. In contrast, combat exposure alone was not significantly associated with overall symptom severity. Both atrocity and combat exposure, however, were significantly related to reexperiencing symptoms. Conclusions: The data suggest that the enduring effect and severity of PTSD symptoms on an individual are associated more with exposure to brutal human death and suffering than the threat of death associated with combat.*

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Several investigators have shown a relationship between the intensity of combat exposure and the subsequent development of posttraumatic stress disorder (PTSD) (1–4). In studies examining the role of particular wartime stressors on postwar adjustment, exposure to atrocities has also been reported to increase the risk of psychological and behavioral disturbance in veterans beyond that associated with exposure to combat (1–6) and has been found to increase the probability of developing PTSD in Vietnam veterans (1, 3, 5). One of these studies showed that participation in atrocities was specifically related to the development of PTSD, while not increasing the risk for development of other psychiatric disorders (5).

Some investigators have suggested that different types of traumatic, war-related experiences may be associated with different symptom patterns or subtypes of PTSD in Vietnam veterans. For example, Laufer et al. (3) demonstrated that combat veterans with PTSD who had participated in atrocities were more likely to have avoidant symptoms than were veterans who had witnessed, but had not participated in, such events. This group also demonstrated that war veterans with heavy combat experience were more likely to show intrusive rather than avoidant symptoms. Differentiating subgroups of PTSD patients by type of stress exposure or symptom profile may explain why certain patients are amenable to some forms of therapeutic interventions, while others remain treatment refractory. It has been shown, for example, that tricyclic antidepressants and monoamine oxidase inhibitors may be particularly useful for treating reexperiencing, but not avoidance, symptoms (7). In contrast, other classes of antidepressants, such as fluoxetine, may be particularly efficacious in treating avoidance symptoms (8).

Although both exposure to atrocities and intensity of combat have each been shown to independently contribute to the development of PTSD, it is not known whether or to what degree these variables affect symptom severity in those veterans who meet criteria for PTSD. Within the group of Vietnam veterans who suffer from PTSD (approximately 15% of combat veterans), there exists a wide range of severity of symptoms. Some individuals are able to maintain productive work and social lives, and others suffer from symptoms that are so debilitating that they are essentially unable to participate in the routine activities of everyday life. The aim of the present study was to investigate the effect of different war stressors (i.e., participation in atrocities and exposure to combat) on severity of chronic PTSD and depressive symptoms in both inpatients and outpatients still seeking and receiving treatment for PTSD symptoms.

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**TABLE 1. Correlations of Stressor Severity Measures and Psychological Ratings for Vietnam Combat Veterans With PTSD**

| | Correlation (r) (df=38) | | | | | |
|---|---|---|---|---|---|---|
| | | | | Impact of Event Scale | | |
| Scale | Hamilton Depression Scale | Mississippi Scale | Figley Scale | Total | Intrusive Subscale | Avoidance Subscale |
| Atrocity Scale | 0.46[a] | 0.70[a] | 0.39[a] | 0.31[a] | 0.46[a] | 0.02 |
| Combat Exposure Scale | 0.10 | 0.07 | 0.10 | 0.09 | 0.34[a] | 0.16 |
| Avoidance subscale | 0.33[a] | 0.08 | 0.41[a] | 0.72[a] | 0.19 | |
| Intrusive subscale | 0.50[a] | 0.53[a] | 0.56[a] | 0.55[a] | | |
| Impact of Event Scale total score | 0.60[a] | 0.40[a] | 0.74[a] | | | |
| Figley scale | 0.53[a] | 0.49[a] | | | | |
| Mississippi scale | 0.66[a] | | | | | |

[a] $p<0.05$, two-tailed t tests.

## METHOD

Forty male Vietnam combat veterans with PTSD (age range=39–48 years; mean=42.3, SD=3.6) according to *DSM-III-R* participated in the study after providing informed consent. Patients fulfilling inclusion criteria were selected from patients consecutively admitted to either an inpatient brief treatment unit or an outpatient clinic and were studied 4 to 8 weeks after seeking treatment. Patients were excluded from study if they had a co-occurring organic, psychotic, or major medical illness or if they were seeking treatment primarily for other comorbid conditions such as substance abuse or affective disorder.

PTSD was diagnosed by consensus, on the basis of information from structured interview data, by using the Structured Clinical Interview for *DSM-III-R* (SCID) (9), reports from the treatment team, and scores on the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (cutoff score=107) (10). The Schedule for Affective Disorders and Schizophrenia (SADS) interview was used to obtain comorbid Research Diagnostic Criteria diagnoses (11).

The Figley Scale for Combat Posttraumatic Stress Disorder (C.R. Figley, R.H. Stretch, unpublished) and the Impact of Event Scale (12) measured symptom severity over the past week. The Mississippi PTSD scale measured both symptom severity and the effects of symptoms on the individual's life. Severity of depression was assessed with the Hamilton Rating Scale for Depression (13). Scores on all four symptom rating scales were intercorrelated (see Results).

The expanded Combat Exposure Scale (14) was used to assess type and frequency of combat exposure. The Atrocity Scale (E. Brett, R. Laufer, unpublished) was used to quantify exposure to and/or participation in particularly traumatic war-related behaviors on a scale of 6–36 (6=no experience of any atrocities, 36=active participation in all). The scale consists of six questions concerning war-related crimes such as torturing and killing of prisoners of war and civilians and mutilation of corpses. Subjects were asked to state whether they had 1) no experience of, 2) heard about, 3) witnessed, or 4) participated in the events. Test-retest reliability was r=0.86 for the Combat Scale and r=0.72 for the Atrocity Scale. Interrater reliability for the Combat Scale was r=0.92 and for the Atrocity Scale, r=0.80. Scores on the combat and atrocity scales were not significantly correlated (r=0.25, df= 38, n.s.).

Differences in symptom severity and severity of stressor between inpatients and outpatients were determined by using Student's t test (two-tailed). The relationship between symptom severity and severity of stressor was determined by using correlational analysis (Pearson's coefficient r).

## RESULTS

Exposure to atrocities and scores on the Mississippi scale were strongly associated (table 1). Atrocity scores were also correlated with scores on the Figley scale and Impact of Event Scale and with current severity of depression as measured by the Hamilton depression scale (table 1). In contrast, exposure to combat was not associated with scores on the Mississippi, Figley, impact of event, or Hamilton scales (table 2). Both atrocity and combat exposure were significantly correlated with scores on the Intrusive subscale of the Impact of Event Scale; neither measure was correlated with scores on the Avoidance subscale (table 1).

Inpatients were comparable to outpatients with respect to level of symptoms as assessed by scores on the Mississippi, Figley, and Hamilton scales, although there was a trend for scores to be higher on the Impact of Event Scale in the inpatient group (table 2). In regard to severity of particular symptom clusters, there was a significantly greater degree of intrusive symptoms in the inpatient group (table 2). Inpatients were similar on combat exposure but showed a significantly greater exposure to atrocities than outpatients (table 2).

## DISCUSSION

This study supports the notion that the type of trauma experienced by an individual, not only the amount, contributes to the severity of PTSD symptoms experienced over the course of the illness and to the impact of these symptoms on overall functioning. These results are consistent with the general notion that both severity and type of stressor may contribute to the course of psychopathology (15) and specifically with studies suggesting a role of exposure to atrocities in the development of PTSD and certain PTSD symptoms. We did not observe specific patterns of avoidance symptoms in veterans exposed to or participating in atrocities, as reported by other investigators (3). However, it may be that treatment-seeking veterans do not have as many avoidance symptoms as veterans selected from the general population.

The relationship between atrocity exposure and scores on the Mississippi scale was found to be particularly robust. The Mississippi scale represents a continuous measure of PTSD symptoms, including the effect of PTSD symptoms on the individual's life, and reflects both acute symptoms of PTSD and long-term or trait aspects of PTSD (10). Because individuals were included only if they had a Mississippi scale score of 107 or greater, the relationship between Mississippi scale scores and atrocity exposure in the present study represents the effect of atrocities on severity of the PTSD.

Scores on the state symptom measures, the Figley scale and Impact of Event Scale, were also positively correlated with atrocity exposure. The Figley scale was developed to measure current symptom severity in combat veterans in the three symptom clusters of PTSD (C.R. Figley, R.H. Stretch, unpublished). The Impact of Event Scale was developed to assess symptoms of PTSD, regardless of the stressor, but it inquires about only two symptom clusters of PTSD (12). Nonetheless, both scales showed a high correlation with each other, suggesting that they tap into similar dimensions of overall state severity.

In the present report exposure to combat was not correlated with overall PTSD symptom severity, whereas other reports have observed stronger relationships between severity of combat exposure and overall PTSD symptoms (1, 10, 16). In other studies, however, combat exposure and PTSD symptoms were assessed in larger groups of veterans, some of whom did not meet diagnostic criteria for PTSD. In the present study, there may have been a narrower range of PTSD symptoms because all veterans met diagnostic criteria for this disorder. Furthermore, the range of combat exposure in the present study was narrower than that in other published reports. Nonetheless, there was a significant correlation between combat exposure and intrusive symptoms, which supports the findings of Laufer et al. (3).

Inpatients and outpatients were compared to each other to determine whether these groups would differ with respect to severity of illness or stressor. Inpatients and outpatients did not differ with respect to total scores on symptom assessment of PTSD. However, inpatients showed a significantly higher level of intrusive symptoms. The higher level of intrusive symptoms in the inpatient group may reflect an overall increase in general distress leading to hospitalization and/or an exacerbation of intrusive symptoms in response to intensive war-focused therapy in the hospital. Inpatients also had a greater degree of exposure to atrocities but not combat, suggesting that exposure to atrocities and attending severity of illness may be more prevalent among veterans seeking inpatient treatment. Alternatively, the inpatient unit may provide an environment more conducive to the safe reporting of atrocities.

**TABLE 2. Scores of Inpatient and Outpatient Vietnam Combat Veterans With PTSD on Measures of Stressor Severity and PTSD Symptoms**

| | Inpatients (N=16) | | Outpatients (N=24) | |
|---|---|---|---|---|
| Scale | Mean | SD | Mean | SD |
| Combat Exposure Scale | 33.4 | 7.5 | 34.2 | 12.9 |
| Atrocity Scale | 17.7[a] | 3.4 | 14.4 | 3.3 |
| Mississippi scale | 128.2 | 16.6 | 124.8 | 15.5 |
| Figley scale | 37.3 | 8.7 | 33.3 | 8.6 |
| Impact of Event Scale | | | | |
| Intrusive subscale | 26.4[b] | 5.3 | 20.0 | 8.0 |
| Avoidance subscale | 19.9 | 7.8 | 20.5 | 9.9 |
| Total | 47.2[c] | 9.0 | 40.5 | 11.2 |
| Hamilton depression scale | 21.9 | 6.6 | 20.2 | 7.8 |

[a] t=3.08, df=37, p<0.005, two-tailed t tests for all comparisons.
[b] t=2.58, df=38, p<0.01.
[c] t=1.93, df=38, p<0.10.

Exposure to atrocities was also particularly related to severity of depression as measured by the Hamilton scale. We have recently reported a higher level of introjective or guilt-associated symptoms of depression in veterans with PTSD than in noncombat veterans with major depressive disorder (17). In addition, within the PTSD group, we found a wide range of guilt-associated symptoms, with some veterans experiencing few guilt-associated depressive symptoms and others experiencing many such symptoms. Clearly, exposure to atrocities has the capacity to evoke profound feelings of guilt, and it may be that veterans who have been exposed to atrocities have a greater tendency to experience symptoms of depression, particularly introjective symptoms.

A possible confounding factor in the present study is that PTSD is an episodic illness, and symptom severity may be more acute in various phases of illness, whereas exposure to combat and atrocities is a constant historical factor. Thus, it is not surprising that the greatest degree of correlation was observed between exposure to atrocities and the Mississippi scale, which taps into longer-term readjustment symptoms. A thorough evaluation of the relationship between stressor and symptom severity may require a multiaxial approach using several instruments and data concerning time course of symptom severity.

Another potential methodological problem in this study concerns the reporting of atrocities. Other investigators have suggested that participation in atrocities may be underreported in Vietnam veterans (1–6). We cannot rule out the possibility that veterans underreported their participation in war crimes, even though they were studied after engaging in treatment. Finally, because the present investigation did not study combat veterans without PTSD, it is not possible to address the question of differential risks associated with the development of a stress disorder following exposure to combat versus exposure to atrocities, as has been addressed in other studies. Nonetheless, the data support the hypothesis that exposure to atrocities plays an important role in the longitudinal course of PTSD.

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# Symptoms of PTSD in 124 Survivors of the Holocaust

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*Objective: Survivors of the Holocaust are expected to be at risk for posttraumatic stress disorder (PTSD), but few empirical data are available. This study investigated PTSD symptoms in Holocaust survivors with well-documented exposure to trauma. Method: The German files of 124 Jewish Holocaust survivors who were judged to be free from bipolar affective disorder, obsessive-compulsive disorder, and organic brain syndrome were selected from those of 145 applicants to West German compensation boards. The psychiatric assessments were reexamined for explicit descriptions of current PTSD symptoms according to the* DSM-III-R *diagnostic criteria. A subgroup of 20 Auschwitz survivors with tattooed identification numbers were also compared with the 45 survivors who had not been in concentration camps. Results: Sixty-three percent of the total sample had been detained in concentration camps, and an average of 78% of their first-degree relatives were reported killed in the Holocaust. Forty-six percent of the total sample met the DSM-III-R criteria for PTSD. The most common symptoms were sleep disturbance, recurrent nightmares, and intense distress over reminders. The tattooed Auschwitz survivors had significantly more symptoms and were three times more likely to meet diagnostic criteria for PTSD than the survivors who had not been in concentration camps. Conclusions: The results suggest a greater risk of chronic PTSD in survivors who were exposed to atrocities. Most survivors had not received adequate psychiatric care.*

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Many survivors of the World War II Nazi concentration camps suffer from chronic psychiatric symptoms (1–8). However, in comparison to Vietnam war veterans, Jewish Holocaust survivors have been virtually neglected by the empirical literature on posttraumatic stress disorder (PTSD). No recent study has explored the full spectrum of their symptoms.

The purpose of this study was to describe symptoms of PTSD (*DSM-III-R*, p. 250) and related phenomena as systematically as possible in a relatively large sample of Jewish Holocaust survivors and to gain an impression of the long-term effects of the concentration camps. Documentation is important for historical reasons. A description of late effects may also contribute to our understanding of the clinical course of PTSD and to the care of other persecuted minorities.

## METHOD

The subjects for this study were 124 Jewish survivors of the Holocaust (58 male and 66 female) whose mean age was 62.0 years (SD=9.4, range=39–86). The minimum entrance criterion for the study, criterion A for PTSD in *DSM-III-R*, was having witnessed atrocities while personally at risk. The subjects were selected out of 145 applicants for German compensation. Because this study was aimed at the symptoms of PTSD, potential subjects with confirmed or suspected organic brain syndrome (N=19), bipolar affective disorder (N=1), and obsessive-compulsive disorder (N=1) were excluded. One subject was included in the total sample but excluded from consideration in the subgroups we describe because of a stay in Auschwitz of less than 1 month. The remaining 123 subjects were divided into three groups. 1) One group (N=78) had been detained in various concentration camps for 1 month or more. 2) A subgroup (N=20) of the concentration camp group had been detained in one extermination camp (Auschwitz) and had been tattooed on the volar side of their left forearms with identification numbers beginning with the letter A. This subgroup had had particularly well-documented exposure to extreme atrocities and threat of death. 3) A third group (N=45) had not been in concentration camps. These subjects had been in labor camps and ghettos or had hidden in the illegal un-

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**TABLE 1. Frequency of the *DSM-III-R* Symptoms of PTSD in 124 Holocaust Survivors**

| | Total Sample (N=124) | | Concentration Camp Survivors (N=78) | | Tattooed Concentration Camp Survivors (N=20) | |
|---|---|---|---|---|---|---|
| Symptom | N | % | N | % | N | % |
| B(1) Intrusive recollections | 69 | 55.6 | 51 | 65.4 | 16 | 80.0 |
| B(2) Recurrent nightmares | 103 | 83.1 | 68 | 87.2 | 18 | 90.0 |
| B(3) Feelings of recurrence | 3 | 2.4 | 1 | 1.3 | 1 | 5.0 |
| B(4) Intense distress over reminders | 93 | 75.0 | 62 | 79.5 | 15 | 75.0 |
| C(1) Avoidance of thoughts and feelings | 48 | 38.7 | 38 | 48.7 | 9 | 45.0 |
| C(2) Avoidance of activities and situations | 62 | 50.0 | 50 | 64.1 | 14 | 70.0 |
| C(3) Psychogenic amnesia | 4 | 3.2 | 3 | 3.8 | 2 | 10.0 |
| C(4) Diminished interest | 80 | 64.5 | 52 | 66.7 | 13 | 65.0 |
| C(5) Detachment | 39 | 31.5 | 29 | 37.2 | 7 | 35.0 |
| C(6) Restricted affect | 35 | 28.2 | 26 | 33.3 | 7 | 35.0 |
| C(7) Sense of foreshortened future | 33 | 26.6 | 22 | 28.2 | 7 | 35.0 |
| D(1) Sleep disturbance | 119 | 96.0 | 77 | 98.7 | 20 | 100.0 |
| D(2) Irritability/anger | 64 | 51.6 | 40 | 51.3 | 10 | 50.0 |
| D(3) Difficulty concentrating | 83 | 66.9 | 53 | 67.9 | 15 | 75.0 |
| D(4) Hypervigilance | 66 | 53.2 | 48 | 61.5 | 14 | 70.0 |
| D(5) Exaggerated startle response | 17 | 13.7 | 11 | 14.1 | 5 | 25.0 |
| D(6) Physiologic reactivity | 75 | 60.5 | 54 | 69.2 | 15 | 75.0 |

derground. They represented a well-documented comparison group with relatively less exposure to atrocities than the tattooed concentration camp survivors. The three groups did not differ significantly in age, sex, or date of assessment.

All 124 subjects were seen by the first author for independent psychiatric examinations requested by German compensation boards. The examination included a 1–2-hour psychiatric interview and a review of the compensation board files. It had been the practice of the psychiatrist to record current symptoms with the assistance of checklists. He was directed by the guidelines of the West German compensation law (9) to examine for exposure to "abuse, characterological sensitization and chronic non-phasic depression." The compensation board files included an affidavit and other documentation of the applicant's persecution and symptoms as well as medical reports submitted by the applicant.

For this study the German-language psychiatric assessments were reviewed for the explicit presence of current PTSD symptoms listed in *DSM-III-R*. For the overall sample the mean time span between the board-ordered assessment and scoring of the record for the study was 7.5 years (SD=5.7, range=0–17). Thirty-eight percent (N=47) of the subjects had been seen within the past 3 years. The date of the psychiatric assessment had no significant effect on whether symptoms met the diagnostic criteria (r=0.14). Symptoms were scored according to the *DSM-III-R* diagnostic criteria. A minimum of one category B symptom, three category C symptoms, and two category D symptoms (table 1) were required for a *DSM-III-R* diagnosis of PTSD.

## RESULTS

The 78 concentration camp subjects (62.9%) had been detained in the camps for a mean of 14.7 months (SD=11.7, range=1–60). Sixty-seven subjects (54.0%) had been in labor camps (mean=26.5 months, SD=14.5, range=2–62); 46 (37.1%) had been in ghettos (mean=25.7 months, SD=12.7, range=2–52); and 28 (22.6%) had been in hiding (mean=16.6 months, SD=15.7, range=1–51). These figures are not exclusive, in the sense that concentration camp subjects had also spent time in ghettos and labor camps. On average, 78% of the first-degree relatives of each subject were reported killed in the Holocaust. A higher percentage of the first-degree relatives of the tattooed subjects (87.7%) than of the subjects who had not been in concentration camps (76.9%) had been killed (t=1.68, df=58, p<0.10).

The mean age of the subjects at the onset of persecution was 19.3 years (SD=6.5, range=3–51). At the time of the examination, 100 (80.6%) of the subjects were married, 14 (11.3%) were widowed, and six (4.8%) were divorced. Data on marital status were incomplete for four subjects (3.2%). One hundred three (83.1%) of the subjects had children, and 20 (16.1%) were childless. For one subject there was no information about parenthood.

All subjects had been referred by German compensation boards through consular offices and were living in the Toronto area. Eighty-six (69.4%) had migrated directly from Europe to Canada. Fifteen (12.1%) had migrated to three countries or more. The subjects were predominantly blue-collar workers. Compared to full-time work status (100%), the mean percentage of time spent at work was 61.9% (SD=26.7%, range=0%–100%).

The subjects had received a mean of 1.7 confirmed medical diagnoses (SD=1.5, range=0–6) since the Holocaust. Thirty-two (25.8%) of the subjects were taking antihypertensive medications, 13 (10.5%) were taking antidyspeptics, 66 (53.2%) were taking analgesics, and 50 (40.3%) were taking other drugs for medical conditions. There was unremitting head pain in 111 (89.5%) of the subjects, gastrointestinal pain in 41 (33.1%), generalized musculoskeletal pain in 39 (31.5%), spinal pain in 37 (29.8%), and chest pain in 14 (11.3%). Sixty-three subjects (50.8%) reported persistent dizziness.

For treatment of psychiatric symptoms, 19 (15.3%) of the subjects were taking antidepressants, 80 (64.5%) were taking benzodiazepines, eight (6.5%) were taking major tranquilizers, and two (1.6%) were taking other psychiatric medications. Twenty-two subjects (17.7%) had received psychotherapy.

The frequency of each symptom of PTSD according to *DSM-III-R* is presented in table 1 for the total sample, for all of the concentration camp survivors, and for the subgroup of tattooed Auschwitz survivors. Fifty-eight (46.8%) of the subjects in the total sample, 40 (51.3%) of the 78 concentration camp survivors, and 13 (65.0%) of the 20 tattooed survivors met the *DSM-III-R* criteria for PTSD.

The tattooed concentration camp survivors had a higher number of PTSD symptoms (mean=9.4, SD=2.4) than did the subjects who had not been in concentration camps (mean=6.7, SD=2.4). This difference was significant ($t=4.16$, df=63, $p<0.001$). Differences between the tattooed survivors and the survivors who had not been in concentration camps were significant for intrusive recollections (80.0% and 40.0%, respectively; $\chi^2=7.35$, df=1, $p<0.007$), for avoidance of activities and situations reminiscent of the trauma (70.0% and 26.7%; $\chi^2=9.10$, df=1, $p<0.003$), and for hypervigilance (70.0% and 40.0%; $\chi^2=3.86$, df=1, $p<0.05$). There was a trend toward a significant difference in physiologic reactivity (75.0% and 46.7%; $\chi^2=3.42$, df=1, $p<0.07$). Although 13 (65.0%) of the 20 tattooed subjects met the *DSM-III-R* criteria for PTSD, only 10 (22.2%) of the 45 subjects who had not been in concentration camps did—a significant difference ($\chi^2=10.46$, df=1, $p<0.002$).

## DISCUSSION

Direct exposure to the Nazi Holocaust surely qualifies as a traumatic experience, and given its magnitude, many survivors are expected to suffer from PTSD. Almost half of our sample of Holocaust survivors met the *DSM-III-R* criteria. Among these, sleep disturbances with nightmares of Holocaust-related content were almost universal. Reminders of the Holocaust evoked intense distress and associated physiologic reactivity in most survivors. Intrusive recollections, avoidance of reminders, difficulty concentrating, diminished interest in the affairs of daily living, hypervigilance, and irritability were present in a majority. Psychogenic amnesia and feelings of recurrence were uncommon (table 1). By comparison, "flashbacks" are common in Vietnam veterans. Perhaps this discrepancy is due to the apparent absence of substance abuse in our sample (10).

Twenty survivors from a notorious extermination camp (Auschwitz) had been tattooed with identification numbers and represented a subgroup with well-documented exposure to extreme atrocities. When we compared them with a group of 45 survivors who had not been in concentration camps, the tattooed Auschwitz survivors experienced more recurrent and intrusive recollections, were more hypervigilant, and made more efforts to avoid activities and situations reminiscent of the camps. The Auschwitz survivors were also three times more likely to meet the diagnostic criteria for PTSD. This difference is all the more remarkable when one considers the number of years that have passed since the Holocaust.

Prolonged exposure to atrocities may produce irreversible effects (1–8, 11). Two studies reported in the past few years also found persistent distress and sleep disturbance in Holocaust survivors (12, 13). In an authoritative paper published 30 years ago, Eitinger (1) described symptoms that resembled those of our sample. He noted that symptoms were particularly severe among prisoners with death sentences. This study presents data that support those findings.

The results of our study should be interpreted with caution. It was not a blind study and our instrument, the list of *DSM-III-R* criteria, has not had norms established to differentiate the effects of catastrophic stressors from the effects of aging. Also, our subjects had been exposed to resettlement and medical illness.

The Holocaust survivors reported a disturbing lack of psychiatric care in spite of our health care system's reputed accessibility. More than half of the subjects were taking benzodiazepines, but only in minimal doses. Less than one-fourth were taking antidepressants or had been in psychotherapy at any time after the war. The reasons for this are unclear. Perhaps survivors avoid a reminder of atrocities in the form of a detailed psychiatric history. Perhaps physicians avoid taking detailed histories of brutality and may therefore not recognize cases of PTSD (14). Perhaps it was demoralization (15) that undermined treatment attempts. Future research may investigate the utilization of health care services by severely traumatized survivors, which has implications for the provision of services and for compliance with treatment.

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*American Journal of Psychiatry* staff will be located in the APA Resource Center and the editorial office in Room 19, Level 1, Convention Center. Hours of operation: Saturday, May 2, noon–5:00 p.m.; Sunday, May 3, 10:00 a.m.–5:00 p.m.; Monday, May 4, through Thursday, May 7, 8:00 a.m.–5:00 p.m. Staff at both locations will be available to schedule office appointments with the Editor, answer authors' questions, and receive papers submitted for publication. The *Journal* publishes only original material that has not been published elsewhere in any form and that is not being considered for publication elsewhere. Five copies are required.

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# Mania Compared With Unipolar Depression in Old Age

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*Objective: The goal of this study was to clarify the meaning and importance of mania in old age. Method: The authors conducted a retrospective study of 50 elderly patients consecutively admitted to a private mental hospital with an index episode of mania. As a comparison group, they used 50 age- and sex-matched patients with unipolar depression. They reviewed the charts of the 100 patients for family history, clinical course, and neurological disorders. Outcome was determined by contacting patients, families, physicians, institutional settings, and vital statistics records. Survival analysis compared mortality rates. Results: The manic patients had a greater familial predisposition to affective disorder and were younger at first psychiatric hospitalization. For the 20 manic patients whose first affective episode was depression, an average of 15 years elapsed before mania became manifest. Eighteen of the manic patients, compared with only four of the depressed patients, had neurological disorders. The manic patients had a significantly higher mortality rate than the depressed patients; by the end of the follow-up, 25 of the manic patients, compared with 10 of the depressed patients, had died. Conclusions: Mania appears to have a poorer prognosis and to be a more severe form of affective illness than unipolar depression. The 18 manic patients with neurological disorders seemed to have "secondary mania." Subtle cerebral changes due to aging may have been responsible for the conversion to mania in the 20 patients who experienced a long latency from first depression to onset of mania. The low frequency of early-onset mania in this study group highlights the need to differentiate early- from late-onset mania.*

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The incidence of first admissions for mania tends to increase with advancing age (1, 2), yet the meaning and importance of mania in old age remains unclear. In contrast, the prevalence of bipolar disorder in the community decreases with age from 1.4% in young adults to 0.4% in those older than 65 years (3). For many elderly manic patients, a latency period averaging as long as 17 years separates the first episode of depression and the onset of mania (4–6). Furthermore, numerous depressive episodes often occur during the latency period. Even among young patients with unipolar depression, Akiskal et al. (7) found that 20% experienced a manic episode within a 6-year follow-up. Therefore, the concept of a unipolar-bipolar dichotomy of affective disorder (8) has been challenged by spectrum and threshold theories that consider mania a more severe form of affective disorder (9, 10).

The average age at onset of affective disorder has been reported to be in the late 40s or 50s in elderly manic patients. Indeed, few elderly subjects with bipolar disorder have suffered from mania before the age of 30 (5). Age at onset may distinguish subgroups of manic patients with different clinical and biological features (11).

In both mania and depression in old age, a good deal of attention has been directed at the role of cerebral-organic factors. Retrospective studies have found an association between coarse brain disorders and mania in old age (4, 5, 12). In a recent prospective study, Broadhead and Jacoby (6) used CT scans to study elderly as well as young patients with mania. They concluded that "organic factors may play an important role in the genesis of affective disorder in old age."

Based in part on the earlier findings of Shulman and Post (4), we hypothesized that, compared with depression in old age, mania in old age 1) is a more severe form of affective disorder, 2) is associated with a preponderance of neurological disorders, and 3) has a poorer prognosis. Usually, depression in old age has

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been studied separately from mania (13, 14). To our knowledge, this is the first reported study comparing elderly manic patients with age- and sex-matched patients with unipolar depression.

## METHOD

Using medical record data, we conducted a chart review of all patients discharged from a private mental hospital in 1980–1987 to identify 50 consecutive admissions of patients 65 years old or older who met *DSM-III-R* criteria for a manic episode. Since the outcome data were recorded in 1990, the minimum follow-up was 3 years and the maximum was 10 years. Subjects with medical problems or cerebral-organic disorders were *not* excluded. For each year's group of manic patients, a comparison group of age- and sex-matched patients who met *DSM-III-R* criteria for major depression were selected. In this way, 50 elderly patients with mania and 50 elderly patients with major depression were included in the study. To select a homogeneous group of depressed patients, patients suffering from bipolar depression at index episode were excluded.

Information was recorded regarding demographic data, family history of affective disorder, and previous psychiatric and neurological history. All geriatric patients at the hospital were routinely assessed by a neurologist. We recorded the presence of a neurological disorder only when the evidence was clearly documented by the clinical consultation note or by a radiologic report. When there was any uncertainty as to the presence or absence of a neurological disorder, consensus was reached by the two raters (K.I.S. and G.M.).

To assess the reliability of the information collected from medical records regarding family history of affective disorder, type of index episode, and presence of preexisting neurological disorder, we compared the ratings of 12 randomly selected patients with blind ratings of the same patients made by one of us (M.T.). For all three variables there was full agreement on the 12 patients.

The number and type of subsequent psychiatric hospitalizations were determined by contacting patients, relatives, physicians, and appropriate institutional settings. The dates of any hospitalization, institutionalization, or death occurring during the follow-up period were recorded. Institutionalization was defined as any placement in a supervised residential setting, including rest homes, homes for the aged, nursing homes, or chronic care settings. Treatment issues were not controlled in this naturalistic study.

To estimate the effects of risk factors simultaneously, logistic regression models (15) and the computerized Statistical Analysis System (SAS) (16) were used. We obtained adjusted odds ratios with 95% confidence intervals.

Survival curves based on the Kaplan-Meier method (17) were used to estimate time to psychiatric rehospitalization, institutionalization, or death. We obtained adjusted hazard ratios (18) and their 95% confidence intervals, controlling for other variables, by using the SAS (19).

## RESULTS

### *Comparison of Patients With Mania and Depression*

Each group was composed of 35 (70%) women and 15 (30%) men. The mean age at index admission of the women in the mania group was 70 years (SD=4.5, range=65–83); the mean age of the women in the depression group was also 70 (SD=4.1, range=65–79). The mean age at index admission of the men in the mania group was 74 years (SD=7.0, range=65–85); the mean age of the men in the depression group was 72 (SD=4.7, range=66–79). No significant differences existed between the subgroups of manic and depressed patients. There was no significant difference in length of follow-up between the mania and depression groups. The mean follow-up period was 5.6 years (SD=2.5, range=3–10). Outcome information regarding mortality was obtained for all 100 patients either by direct contact with patients and families or by referring to the official vital statistics records.

Eighteen (36%) of the manic patients had evidence of neurological disorders, compared with four (8%) of the depressed patients. The difference was statistically significant after adjusting for age, sex, and previous episodes (adjusted odds ratio=8.0, 95% confidence interval=2.3–27.4, p=0.001). Table 1 lists the type of neurological disorders evidenced by the 18 manic patients. Because of the retrospective nature of the study we did not attempt to establish an exact temporal relationship between first episode of mania and cerebral-organic disease.

The manic patients had a significantly higher mortality rate than the depressed patients (adjusted hazard ratio=2.4, 95% confidence interval=1.1–11.8, p=0.02) after controlling for age, sex, previous episodes, and neurological disorder. At the end of the follow-up, 25 (50%) of the manic patients were dead compared with 10 (20%) of the depressed patients. Figure 1 shows that the probability of remaining alive after 5 years of follow-up was approximately 90% for patients with unipolar major depression and 65% for patients with mania. By 10 years the probability of remaining alive for each group was 75% and 30%, respectively. With the use of survival curves we can estimate the probability of remaining alive for 10 years after being alive for 5 years; for manic patients this probability was 54% (0.35 divided by 0.65) and for depressed patients it was 82% (0.70 divided by 0.85). Only one death by suicide was reported—that of a patient with unipolar depression—in the entire study group.

The depressed patients had a shorter time to institutionalization (adjusted hazard ratio=3.6, 95% confidence interval=1.1–5.4, p=0.02) after controlling for age, sex, previous episodes, and neurological disorder. At follow-up, 18 (37%) of the 49 depressed patients were institutionalized compared with 13 (30%) of 44 manic patients. (Patients who died while institutionalized were included in this analysis.)

Twenty-six (52%) of the manic patients compared

**TABLE 1. Demographic and Clinical Data for 18 Elderly Patients With Mania and Neurological Disorders at Index Hospitalization**

| Patient | Sex | Family History of Affective Disorder | Age at Onset of Affective Disorder (years) | Age at First Manic Episode (years) | Neurological Disorder |
|---|---|---|---|---|---|
| 1 | M | Negative | 82 | 82 | Chronic alcoholism, peripheral neuropathy |
| 2 | F | Positive | 20 | 20 | Frontal lobotomy, bilateral encephalomalacia |
| 3 | F | Negative | 50 | 50 | Chronic alcoholism, dementia |
| 4 | F | Negative | 67 | 67 | Chronic alcoholism, seizures/delirium |
| 5 | M | Negative | 69 | 70 | Chronic alcoholism, blackouts/delirium |
| 6 | M | Negative | 68 | 68 | Cerebral contusions |
| 7 | F | Positive | 41 | 46 | Parkinson's disease |
| 8 | F | Negative | 39 | 43 | Right cerebral infarct |
| 9 | F | Negative | 83 | 83 | Multiple cerebral infarcts |
| 10 | F | Negative | 43 | 58 | Encephalopathy/neuroleptic malignant syndrome |
| 11 | M | Negative | 58 | 58 | Closed head injury |
| 12 | M | Negative | 80 | 80 | Recurrent cerebral contusions (boxing), lacunar infarct |
| 13 | F | Positive | 71 | 71 | Left cerebral hemorrhage 20 years before onset of affective disorder |
| 14 | F | Positive | 39 | 39 | Cerebral infarct |
| 15 | M | Positive | 84 | 85 | Dementia |
| 16 | M | Negative | 76 | 76 | Embolic cerebral infarct, mild dementia |
| 17 | F | Negative | 19 | 19 | Right capsular necrosis, cerebral vasculitis (rheumatoid) |
| 18 | F | Positive | 68 | 68 | Parkinson's disease |

with 16 (32%) of the depressed patients had a positive family history of affective disorder in a first-degree relative (odds ratio=2.3, 95% confidence interval=1.01–5.2, p=0.04).

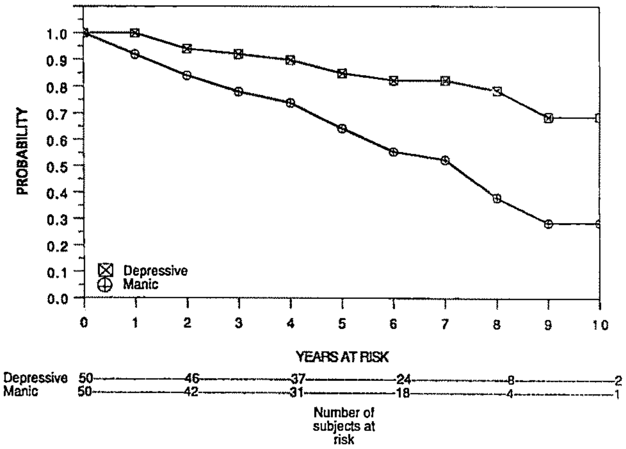
The manic patients were significantly younger at first psychiatric hospitalization than the depressed patients (two-tailed t test=2.3, df=98, p=0.02). The mean age at first psychiatric hospitalization of the depressed patients was 62.7 years (SD=11.0, range=34–79). For the manic patients the mean age at first psychiatric hospitalization was 55.5 years (SD=18.8, range=19–84).

### *Manic Patients*

Twenty-three (46%) of the manic patients were rehospitalized in a psychiatric unit at least once during the follow-up period. Having a neurological disorder at the time of the index admission was a predictor of subsequent psychiatric hospitalization (odds ratio=4.6, 95% confidence interval=1.1–19.2, p=0.05) after adjusting for sex, age, previous episodes, and age at first manic episode. Neurological disorder also predicted institutionalization (adjusted odds ratio=7.7, 95% confidence interval=1.2–48.1, p=0.03) after adjusting for age, sex, and previous episodes. Twelve (24%) of the manic patients were institutionalized during the follow-up period.

Unlike Shulman and Post (4), we found no significant sex differences between the manic and depressed patients with respect to neurological disorders. In addition, an age at onset of more than 55 years predicted a shorter time in remission until first psychiatric rehospitalization (adjusted hazard ratio=3.9, 95% confidence interval=1.2–13.5) after controlling for age, sex, neurological disorder, and previous episodes. Six (33%) of the 18 neurologically impaired manic patients had a positive family history of affective disorder in first-degree relatives (table 1), compared with 26 (52%) of all 50 manic patients ($\chi^2$=4.6, df=1, p=0.03).

**FIGURE 1. Cumulative Probability of Death for 50 Elderly Patients With Mania and 50 Elderly Patients With Unipolar Depression at Index Hospital Admission**



Twenty (40%) of the manic patients experienced depression as their first affective episode at a mean age of 47.5 years (SD=18.3, range=19–84). The mean latency from first depression to first mania in these 20 patients was 14.9 years (SD=5.1, range=1–48). There was a significant difference in mean age at first mania between men (mean=58.7, SD=16.6, range=19–83) and women (mean=68.7, SD=13.2, range=42–85) (t=2.05, df=47, p=0.04).

The clinical course of six manic patients was characterized by manic episodes but not depressive episodes before the index admission.

### *Depressed Patients*

Not surprisingly, older age predicted higher mortality in the depressed patients (adjusted hazard ratio=1.2, 95% confidence interval=1.0–1.4, p=0.02) after controlling for sex, previous episodes, and neurological disorder. Also, depressed patients who had been institutionalized before the index episode had a higher mortality (adjusted odds ratio=17.2, 95% confidence interval=1.0–287.7, p=0.05) after controlling for age and sex. In addition, nonmarried status predicted institutionalization for the depressed patients (adjusted odds ratio=4.7, 95% confidence interval=1.2–18.6, p=0.02) after controlling for age and sex.

## DISCUSSION

This study supports a number of hypotheses and findings of earlier studies of elderly manic patients (4–6). In particular, the prevalence of cerebral-organic disorder was found to be significantly higher in manic patients (36%) than depressed patients (8%). Neurological disorders were heterogeneous in nature and nonspecific with regard to brain location. As in previous studies, the prevalence of Alzheimer-type dementia was no higher than the expected proportion in the general population. Alcohol-related disorders accounted for four of the 18 cases of neurological impairment in the manic patients, and cerebrovascular disease was evident in six of the 18 patients. Despite the uncertain relationship of neurological disorder to the onset of mania, a unique pattern appears to be evident in these 18 patients. The age at first mania and age at onset of affective disorder were the same or very close temporally in these patients. They seemed to fit the category of patients with "secondary mania" described by Krauthammer and Klerman (20), associated with a relatively lower rate of genetic predisposition to affective disorder. This is in marked contrast to the long latency from first depression to manic episode for many of the elderly manic patients who did not have evidence of neurological disorder.

Manic patients experienced a poor outcome, suffering a significantly higher mortality rate. Half of the manic patients were dead after almost 6 years of follow-up, compared with 20% of the depressed patients. This high mortality rate has not been reported in follow-up studies of patients with early-onset mania (21). The higher mortality rate among manic patients may account for the relatively shorter time to institutionalization for depressed patients.

For elderly manic patients whose first psychiatric hospitalization was for depression, an average of 15 years elapsed before mania became manifest. This is suggestive of a "conversion" that may be due to factors different from those operating in patients with obvious neurological disorders. It should be emphasized that this retrospective study used coarse measures of cerebral-organic disorder. Therefore, we may have underestimated the true role of cerebral dysfunction, especially subtle cerebrovascular pathology. With newer imaging techniques such as magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, this issue can be studied more accurately.

Genetic loading may be more of a factor in elderly manic patients than in elderly depressed patients. Although genetic factors are generally considered to play a less prominent role in old age (22), mania has been associated with a higher prevalence of positive family history than has unipolar depression (23). We found a higher proportion of manic patients with a positive family history of affective disorder (52%) than has been reported in other studies (5, 6, 12). However, we applied the same assessment measures to the depression comparison group and found that only 32% had a positive family history. The manic patients had an earlier age at onset of first psychiatric hospitalization than the depressed patients. An earlier age at onset is associated with a positive family history (5, 6). Even in old age, manic patients appear to be genetically predisposed to affective disorder but perhaps less so than young manic patients (23).

Overall, age at onset of mania was late in life (mean=55.5 years), a finding that is consistent with other studies of old age (4, 5). The average age at onset of "early-onset" mania found in other studies was 29 years (23, 24). Indeed, only three of our 50 elderly manic patients had suffered from mania when they were younger than 30. A study of university clinic outpatients (25) compared elderly patients with young depressed patients and found a higher prevalence of mania in the younger patients—7.3% versus 1.4%. Does the young patient with bipolar disorder burn out (26) or is there a high mortality rate? This raises questions about fundamental differences between early-onset and late-onset mania.

Our data are consistent with the spectrum theory of Akiskal (9) and the threshold theory of Tsuang et al. (10), which consider mania a more severe form of affective disorder. Controlled studies of the treatment of mania, particularly with lithium carbonate, are needed to explore the hypothesis that mania in old age represents a manifestation of greater CNS vulnerability (27).

As a group, the 50 elderly manic patients in this study had a genetic predisposition to affective disorder that became manifest relatively late in life. This applies especially to the manic patients without coarse brain disorders. With growing interest in elderly manic patients, greater numbers of patients will be available for study. Furthermore, the advent of new technologies (28, 29) and advances in our conceptualization of affective disorders should help to clarify the special meaning and importance of mania in old age. We have highlighted two distinct subgroups of patients with mania in old age: 1) patients whose first episode of affective disorder is depression and who have a long latency period before they experience their first episode of mania and 2) those suffering from secondary mania associated with neurological disorders, whose mania is often their first affective episode or follows closely after their first episode of depression. Further studies of mania in the elderly should focus on its distinct nature compared with depression and its fundamental difference from mania that begins early in life.

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# Correlates of Persistent Depressive Symptoms in Widows

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*Objective: Delineation of factors that predict depressive symptom severity 6 or more months after the loss of a spouse may help identify individuals at risk for persistent depressive symptoms. In this study, sociodemographic and clinical correlates of depressive symptom severity were examined among widows 6 to 16 months after the deaths of their husbands. Method: The 50 subjects were identified from the Allegheny County, Penn., death records and were interviewed by telephone. The authors examined the relationship of depressive symptoms to sociodemographic variables, perceptions of sex role and quality of social supports, level of support sought for bereavement, and premorbid personal and family psychiatric history. Results: Widows with persistent depressive symptoms were less likely to have worked outside the home, had less favorable perceptions of their interpersonal support systems, were more likely to have had previous psychiatric disorders, and were likely to have sought professional help in response to their bereavement. In a multivariate model, only premorbid psychiatric history and the perception of interpersonal support system made independent contributions to the prediction of Beck Depression Inventory scores above the normal range. Conclusions: These results suggest several factors that may identify women at risk of protracted psychiatric morbidity after their husbands' deaths. They also suggest that the persistence of depressive symptoms an average of 1 year after the loss of a spouse may reflect a pathological condition rather than normal grieving.*

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As our national population ages, spousal bereavement is becoming an increasingly important source of psychiatric morbidity. Newly bereaved individuals typically respond to their losses by exhibiting depressive symptoms that are often sufficient in number and severity to be indistinguishable from primary affective disorders (1–4). However, several lines of epidemiologic evidence suggest that bereavement-related depression may be distinct from other forms of depressive illness. Unlike major depression, depression within 1 month of the death of a spouse is not more common in women than men, does not appear to increase in frequency with advancing age, and is not associated with a previous personal or family history of depression (2). The suggestion that bereavement-related depression differs in its pathophysiology from other depressive disorders (1–4), the rarity of self-destructive or psychotic symptoms in bereaved individuals (1–4), and the encouraging observation that bereavement-related depression most often resolves spontaneously (1, 3) have led most clinicians to be conservative in their management of this condition.

Bereaved patients who have persistent depressive symptoms present a diagnostic dilemma. This diagnostic issue is addressed in *DSM-III-R,* which states that prolonged and marked functional impairment suggests the bereavement is complicated by the development of a major depression. However, recognizing the interindividual and transcultural variations in the duration of what is considered to be a normal bereavement period, *DSM-III-R* does not provide specific guidelines regarding duration. The delineation of factors that predict depressive symptom severity 6 or more months after the loss of a spouse may help to identify individuals at risk for persistent depressive symptoms and to detect and treat complicating major depression.

In the current study, we assessed the number and severity of depressive symptoms among 50 widows whose husbands had died 6 to 16 months previously. The relationships of sociodemographic and clinical variables to persistent depressive symptoms were examined with the goal of better understanding the nature of bereavement-related depressive symptoms that persist an average of 1 year after the loss of a husband.

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## METHOD

### *Selection of Subjects*

An alphabetical listing by surname of widows whose husbands had died between 6 and 16 months before the study was generated from the Allegheny County, Penn., death records (Carnegie Library of Pittsburgh, Vital Statistics Department). The first 188 of these names were cross-checked against all telephone directories for Allegheny County, and current listings for 120 widows were identified. The remaining 68 were dead, had moved outside Allegheny County, or were no longer listed in the telephone directories for unknown reasons. Of these 120 widows, 72 were contacted in alphabetical order to produce a target sample of 50 widows who were fluent in English and willing to participate in the study. This 69% rate of participation was similar to rates found in previous studies of bereavement (2, 5). Written informed consent was obtained by mail, and confidentiality was maintained through the use of a data base organized according to a numerical identification system. This study was approved by the Psychosocial Institutional Review Board of the University of Pittsburgh.

### *Sociodemographic and Clinical Assessments*

Sociodemographic and clinical information was obtained from each subject through a semistructured telephone interview administered by a mental health nurse with specialized experience in geriatric psychiatry. Each interview included the administration of a sociodemographic questionnaire, the Beck Depression Inventory (6), the Interpersonal Support Evaluation List (7), and the Bem Sex Role Inventory—Short Version (8). All three instruments are self-evaluative and have been validated for use across the adult age spectrum in clinical and nonclinical populations. Each self-report item was presented verbatim in the order in which it appeared in the respective instrument. The individual telephone interviews averaged approximately 30 minutes.

Our pilot studies and a previously published methodological study of bereaved elders (9) indicated that, compared to mailed questionnaires, telephone interviews make potential subjects more comfortable with providing sensitive information and result in greater subject compliance and less likelihood of inadvertent omissions. Previously published studies of bereaved elders (5, 9, 10) did not indicate systematic differences in responses on self-report instruments designed to assess depression or other bereavement-related feelings or behaviors when the instruments were administered in person or through mailed questionnaires. Furthermore, the telephone interview provided an opportunity for a mental health professional to clarify the questions about onset of depressive symptoms and about personal and family psychiatric history. Comparisons of the quality of data obtained from community samples by telephone and by personal interviews (11–15), including information about depressive symptoms and social functioning (15), have revealed few differences between these two methods.

The sociodemographic questionnaire included age, telephone number, race, religion, highest level of education completed, work history, annual income, number of children, and date of husband's death. In addition, this questionnaire elicited information on the level of support sought in response to the loss of the subject's husband and her previous personal and family history of psychiatric disorders. The level of support sought in response to bereavement was elicited by the question, "Since your husband's death, have you talked with anyone about your feelings and/or problems?" If the response was "yes," the subject was asked whether this was best described as support from friends, family, or clergy; one contact with a mental health professional; more than one outpatient mental health contact; or inpatient psychiatric treatment. The level of support sought for bereavement was rated from 1 to 4, from the least to the most intensive. A global assessment of each subject's premorbid personal and family psychiatric history was elicited by the question, "Have you or any member of your family ever seen a doctor, nurse, counselor, social worker, or therapist for emotional, psychological, or nerve problems, before the loss of your husband?" If the answer was "yes," the subject was asked to specify the individual as herself or to state the relationship of the affected family member(s) to her. This method of determining the presence of a premorbid personal history or family history of psychiatric disorder was chosen because it is efficient and provides few false positives (16–18). Individuals identified by personal reports and those of family members as having received treatment by mental health professionals almost always have authentic psychiatric disorders (16–18). However, underreporting of episodic or less debilitating psychiatric disorders is an inherent limitation of the family history method, even when consensus diagnoses are made from information obtained from multiple informants and ancillary sources (16–18).

An assessment of the number and severity of depressive symptoms was made by using the Beck Depression Inventory. This multiple-choice inventory includes 21 items, each of which corresponds to a depressive symptom and is followed by four self-evaluative statements. The statements are weighted to indicate the severity of each symptom, from absent (0) to severe (4), and they are summed to produce a total score. In this way, the total Beck score is weighted for both the number and severity of depressive symptoms. A total score less than 10 reflects euthymia or minimal depressive severity (19). For each widow who endorsed depressive symptoms, a best assessment of the time of onset was made.

The Beck Depression Inventory served as the principal dependent variable in our study. It provided an index of the number and severity of depressive symptoms, and we used it, rather than a structured diagnostic interview, because *DSM-III-R* does not provide operationalized criteria for distinguishing "uncomplicated" bereavement from major depression. However, each of the nine *DSM-III-R* symptom criteria for major depression is addressed by at least one of the items included in the Beck inventory (depressed mood: Beck items 1, 10, 11; diminished interest or pleasure: items 4, 12; weight or appetite change: items 18, 19; sleep disturbance: item 16; psychomotor retardation: item 15; loss of energy: items 15, 17; feelings of worthlessness or guilt: items 3, 5–8; inability to concentrate or indecisiveness: item 13; suicidal ideation: item 9). Ignoring the *DSM-III-R* criteria for uncomplicated bereavement, we used these data to assess whether the criteria (five of nine symptoms) for major depression were met.

The Interpersonal Support Evaluation List consists of 40 true-false statements and assesses the perceived availability of supportive resources. The items are divided equally into 20 positive and 20 negative statements. One point is assigned for each answer indicating the availability of a particular resource, and the total score ranges from 0 to 40.

The Bem Sex Role Inventory—Short Version was designed to rate an individual's sex role orientation on a continuum from "feminine" to "masculine." It includes 20 gender-specific characteristics (10 masculine, 10 feminine) and 10 gender-neutral items. This instrument is based on the traditional concept of femininity, i.e., derivation of personal fulfillment from dedication to others, and characteristic traits include passivity, dependence, helplessness, and submissiveness. In contrast, assertiveness, dominance, self-reliance, and independence are examples of the masculine traits included in the instrument. Each description is rated on a 7-point scale to reflect the extent to which the item is considered a desirable personal trait. Raw and standard scores for both the masculinity and femininity subscores are derived from the 20 gender-specific characteristics. Single t scores are then assigned on the basis of the difference in the standardized subscores (femininity minus masculinity) and range from 12 to 88 (12–50=masculine range, 51–88=feminine range). Bem (20) suggested that women whose personalities include a combination of traditional feminine and masculine traits (lower scores) are more adaptive than those who exclusively endorse traditional feminine traits.

### *Statistical Analysis*

Mean values were compared by using two-tailed t tests, and categorical variables were compared by means of the chi-square statistic or Fisher's exact test, as appropriate. Associations of sociodemographic and psychometric characteristics with the Beck score were explored with parametric Pearson or nonparametric Spearman correlation coefficients, as appropriate.

A multivariate model predicting the severity of depressive symptoms from the sociodemographic and clinical variables included in this study was calculated by using the stepwise multiple logistic regression method. A widow was characterized as depressed if her Beck score was 10 or higher and as not depressed if her Beck score was less than 10. According to Beck et al. (19), this cutoff separates nondepressed subjects or those with minimal depression from those with at least mild depression.

## RESULTS

The mean age of the study group was 68.5 years (SD=8.7), and the mean duration of widowhood was 11.6 months (SD=2.7). Most widows were living on retirement incomes; of the 48 widows who responded to this question, 44 (91.7%) had annual incomes of $20,000 or less. A total of 38 (76.0%) had completed at least a high school education, and 46 (92.0%) of the women had worked outside of the home at some time in their lives. The group studied was almost exclusively Caucasian (two of the 50 were black), and 46 (93.9%) of 49 respondents were Catholics or Protestants. The widows in the study had given birth to an average of 2.3 children (SD=1.8). The average perceived availability of interpersonal support was reflected by a mean score on the Interpersonal Support Evaluation List of 34.8 (SD=5.2).

The study group was compared to the population data for females in Allegheny County provided by the 1980 census (21). However, the data available for comparison must be viewed as estimates because widows are not separated as a group in the census. In 1980, 88.5% of the population of Allegheny County was white, 10.3% was black, and 1.2% was composed of other racial groups. Assuming that this racial distribution exists currently and is similar for widows, 44 whites and six nonwhites would have been expected in our sample of 50 widows. Forty-eight whites and two blacks were actually included, a proportion that did not differ significantly from that expected from the census statistics (Fisher's exact test, p=0.27). According to the 1980 census, 32.0% of the women living in Allegheny County who were at least 25 years of age had less than a high school education, 44.5% had completed high school, and 11.9% had completed a college or graduate degree. The respective percentages from our sample of widows were similar: 24.0% (N=12) had not completed high school (p=0.50, Fisher's exact test), 46.0% (N=23) had graduated from high school (p=1.00, Fisher's exact test), and 6.0% (N=3) had completed college (p=0.49, Fisher's exact test). Relevant data on the employment status and annual income of widows in Allegheny County were more difficult to extract from the census and were further complicated by retirement. In 1980, 6.6% of the women living in Allegheny County who were at least 65 years of age were employed full-time, compared to 4.0% (N=2) in the study sample (p=1.00, Fisher's exact test). However, an additional 12.0% of the widows in the study (N=6) were engaged in part-time employment, and no comparative data on part-time employment were available. In addition, the average annual income in 1980 for women who were at least 65 years of age and living in Allegheny County was $13,696, and the average income of female heads

**TABLE 1. Correlations of Sociodemographic and Clinical Variables With Beck Depression Inventory Scores of 50 Widows**

| Variable | Correlation With Beck Score: Coefficient | p |
|---|---|---|
| Age | 0.143[a] | 0.16 |
| Duration of widowhood | 0.004[a] | 0.49 |
| Level of education | –0.048[b] | 0.37 |
| Employment history | –0.380[b] | 0.003 |
| Annual income | 0.010[b] | 0.47 |
| Level of support sought for bereavement | 0.402[b] | 0.002 |
| Interpersonal Support Evaluation List score | –0.396[a] | 0.002 |
| Bem Sex Role Inventory score | 0.018[a] | 0.45 |

[a] Pearson correlation coefficient.
[b] Spearman correlation coefficient.

of households (by virtue of divorce or widowhood) was $11,451. Both of these averages are in the middle of the range for the widows in the study sample. Furthermore, the mean Bem Sex Role Inventory score for the widows, 69.9 (SD=10.3), was in the middle of the femininity scale, which ranges from 51 to 88. In summary, the study sample appeared to be reasonably representative of widows in Allegheny County, to the extent that we could assess this from census information.

The mean Beck depression score for the 50 widows was 7.4 (SD=5.4, range=0–30). Twelve (24.0%) of the 50 had scores of 10 or higher, beyond the upper limit of the range for euthymia or minimal depression. The mean Beck depression score of this group of 12 widows was 14.6 (SD=5.6), whereas the mean score for the residual group was 5.1 (SD=2.7). The validity of the cutoff score for the Beck Depression Inventory was evaluated by determining the proportions of widows in the two groups who fulfilled the *DSM-III-R* symptom criteria for major depression, each of which is addressed by one or more items on the Beck scale. Ten (83.3%) of the 12 widows whose Beck scores were 10 or higher met the *DSM-III-R* symptom criteria for major depression, and the remaining two widows endorsed at least three of the five depressive symptoms required to satisfy these criteria. In contrast, only one (2.6%) of the 38 widows whose Beck scores were less than 10 met the *DSM-III-R* symptom criteria for major depression (p=0.000, Fisher's exact test). All of the widows who endorsed depressive symptoms at the time of inclusion in our study dated the onset of the symptoms to the deaths of their husbands; this finding is consistent with the results of previous prospective, longitudinal studies of spousal bereavement (1, 3).

Six (12.0%) of the 50 widows stated they had received psychiatric treatment before the loss of their spouses. Three (6.0%) of the widows had first-degree relatives who had been treated for psychiatric disorders. Twenty subjects (40.0%) sought emotional support in response to the loss of their husbands; five (10.0%) contacted mental health professionals, and two (4.0%) remained in sustained outpatient therapy. In no case did loss of a husband lead to inpatient treatment for bereavement.

**TABLE 2. Stepwise Multiple Logistic Regression Model Predicting Beck Depression Score of 10 or Higher From Sociodemographic and Clinical Variables of 50 Widows[a]**

| Variable | Odds Ratio | 95% Confidence Interval | Improvement Chi-Square (df=1) | p |
|---|---|---|---|---|
| Premorbid psychiatric history | 19.7[b] | 1.25–308 | 10.73 | 0.001[c] |
| Interpersonal Support Evaluation List score | 1.2[b] | 1.02–1.50 | 4.01 | 0.05[c] |
| Family psychiatric history | 19.9 | 0.79–504 | 3.38 | 0.07 |

[a] Stepwise multiple logistic regression was performed with 0.10 and 0.15 confidence limits for entry and removal, respectively, of premorbid psychiatric history, family psychiatric history, and the variables listed in table 1.
[b] Statistically significant odds ratio.
[c] Statistically significant contribution to goodness-of-fit of model.

Correlation coefficients describing the associations of sociodemographic and clinical characteristics with the scores on the Beck Depression Inventory are presented in table 1. A history of work outside of the home and the perceived availability of interpersonal support were significantly negatively correlated with the continuous Beck score. Not surprisingly, the level and intensity of support sought for bereavement exhibited a significant positive correlation with the Beck score. Widows who reported personal psychiatric histories before the loss of their husbands had a mean Beck score of 15.2 (SD=7.9), which is in the moderately severe range, whereas those who had no such history had a mean Beck score that was less than half of this value, 6.3 (SD=4.0) (t=4.45, df=48, p=0.000). The mean Beck depression score was not significantly higher in the subjects who had first-degree relatives with histories of psychiatric disorders (mean=10.0, SD=5.3) than among the women without such relatives (mean=7.2, SD=5.4) (t=0.87, df=48, p=0.39). However, the latter comparison was limited by the small number of widows who had family psychiatric histories (N=3).

We used stepwise multiple logistic regression to determine which of the sociodemographic and clinical variables independently contributed to the prediction of widows who had Beck scores above the normal range (10 or higher), while controlling for the other variables. A best-fitting model was calculated by using confidence units of 0.10 and 0.15 for entry and removal of variables from the stepwise procedure. A description of the resulting model is presented in table 2. The presence of a premorbid psychiatric history and the perception of inadequate social supports emerged as independent predictors of Beck scores above the normal range. Specifically, the likelihood of an abnormal Beck score an average of 1 year after the husband's death was 20 times as high among women with premorbid psychiatric histories as among widows without such histories. In addition, each 1-point increase in the score on the Interpersonal Support Evaluation List increased the likelihood of having an abnormal Beck score by 20%. The presence of a family psychiatric history tended toward an independent contribution to the goodness-of-fit of the model, although the odds ratio associated with this variable did not reach statistical significance.

## DISCUSSION

Some discussion of the dependent variable of the study seems warranted to place the findings into perspective. We chose the Beck Depression Inventory, which provides a continuous index of the number and severity of depressive symptoms, rather than a structured diagnostic instrument designed to provide a *DSM-III-R* diagnosis of major depression because previous studies of bereavement-related depression have not used the same diagnostic systems and because *DSM-III-R* does not provide clear diagnostic criteria for distinguishing this disorder from uncomplicated bereavement. With the possible exceptions of psychomotor retardation, morbid guilt, or suicidal ideation, a full range of depressive symptoms is common in the first year after the death of a spouse (1–4). Moreover, *DSM-III-R* does not provide a limit for the duration of uncomplicated bereavement.

The persistence of depressive symptoms after the death of a spouse often raises the clinical suspicion that a major depression has emerged, but there is little empirical evidence in the literature to guide the application of this commonly held view. In their prospective, longitudinal study of older bereaved widows and widowers, Bornstein et al. (3) found that the prevalence of depression defined according to the Feighner criteria (22) was 35% at 1 month and 17% at 13 months, and 13% of the subjects were depressed for the entire year. Retrospective or cross-sectional estimates of the prevalence of major depression (*DSM-III-R* symptom criteria) in bereaved widows have been 28% (23) to 32% (5) at 6 months and 27% (5) at 1 year after the death of a spouse. Although most bereaved individuals fail to fulfill diagnostic criteria for a full depressive syndrome as early as 1 month after the death of the spouse, a substantial fraction are depressed at 1 month and remain so 1 year later.

The Beck Depression Inventory is a widely used self-report instrument that has been validated as a measure of depressive symptoms in clinical and nonclinical populations across the age spectrum (6, 19). Several lines of evidence also support the use of the Beck cutoff of 10 for bereaved widows. Eleven (22.0%) of the 50 widows in our study exhibited a sufficient number of depressive symptoms to fulfill the *DSM-III-R* symptom criteria for major depression, and this rate falls within the range (17% to 27%) of previously published prevalences for depression 1 year after a spouse's death. Of these 11 widows, ten (90.9%) had Beck scores of at least 10. Furthermore, Reynolds et al. (24) recently reported that the EEG sleep recordings of bereaved subjects who met the Research Diagnostic Criteria (RDC) (25) for major depression resembled those of elderly patients with recurrent unipolar major depression, and the recordings of nondepressed bereaved subjects were similar to those of elderly comparison subjects. The mean Beck scores of the depressed and nondepressed bereaved subjects included in the sleep study, 15.2 (SD=6.2) and 5.1 (SD=4.7), were similar to those of the widows in the current study, who were categorized as depressed according to the Beck cutoff score of 10.

The principal findings of the current study were that employment history, level of support sought for bereavement, perception of social support system, and premorbid psychiatric history all exhibited significant univariate associations with the severity of persistent depressive symptoms in widows bereaved for an average of 1 year. Several of these results support the findings of previous studies. Jacobs et al. (5) found that unemployment was more common among bereaved individuals who met the *DSM-III-R* symptom criteria for major depression 6 to 12 months after the loss of their spouses than among those who were not depressed, although this observation was confounded by a gender effect that was not present in our study. Whether this association derives from a protective effect of employment or from the fact that depression may lead to the inability to work cannot be determined from our data. We found no previous studies that assessed the relationship of the level of emotional support sought for bereavement to the severity of persistent depressive symptoms. However, Raphael (26) found that supportive psychotherapy provided to widows for 3 months after the deaths of their husbands significantly reduced the level of psychiatric morbidity 13 months later. In this intervention study, the perception of nonsupportiveness in the social network was hypothesized to be a risk factor for persistent psychiatric morbidity and predicted greater response to psychotherapeutic intervention.

In previous studies that examined bereaved individuals as long as 13 months after the deaths of their spouses (1–5), premorbid psychiatric history was not associated with the clinical diagnosis of depression. However, in our study of widows whose husbands had died 6 to 16 months previously, this variable made an important contribution to the severity of persistent depressive symptoms. This difference suggests that the persistence of major depressive symptoms beyond 1 year may reflect the exacerbation of a premorbid psychiatric disorder, a criterion embodied in the differential diagnosis of bereavement and major depression in the RDC but not *DSM-III-R*.

Because it was recognized that the sociodemographic and clinical variables used in our study might not act independently in the prediction of persistent depressive symptoms, a multivariate analysis was performed to determine which variables made independent contributions to the prediction of Beck scores of at least 10. Only premorbid psychiatric history and the score on the Interpersonal Support Evaluation List, two of the four variables identified in the univariate analyses, made significant independent contributions to the goodness-of-fit of the multiple logistic regression model. As described in the Results section, both of these factors were strongly associated with persistent depression, reflected by Beck scores of at least 10, an average of 1 year after the deaths of their husbands.

Although our findings must be interpreted in the context of the limitations of the methods used and may not be generalizable to other populations, they suggest four sociodemographic and clinical variables that may identify widows who are at risk for persistent depressive symptoms after the deaths of their husbands. Furthermore, our results provide the first empirical evidence supporting the view that the persistence of major depressive symptoms beyond 1 year after the death of a spouse may reflect a pathological rather than a normative condition.

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# Quantitative Assessment of the Behavior of Psychotherapy Supervisors

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*Objective: The aim of this study was to explore the behavior of psychotherapy supervisors by using the Psychotherapy Supervision Inventory. Method: The authors used the Psychotherapy Supervision Inventory to rate 53 videotaped supervision sessions of 34 different supervisors. They also used the variable of the rater's perception of the excellence of the supervisor as a teacher. The data were subjected to a cluster analysis and a K-means analysis. Discriminant function analyses were applied to the comparison of the behavior of 19 supervisors with two different residents and the behavior of all 34 supervisors with residents in three different years of training. The relationship between rater-perceived excellence and Psychotherapy Supervision Inventory scores was analyzed by using stepwise multiple regression. Results: There was a high level of agreement among the four raters' judgments of supervisors' excellence. Empathy accounted for 72% of the variance in rater-perceived excellence and focus on the therapist accounted for an additional 5%. When empathy was dropped from the equation, experiential orientation accounted for 60% of the variance in ratings of excellence, clarification and interpretation accounted for an additional 16%, and depth accounted for another 3%. Conclusions: In the context of established relationships, supervisors have stable behavior patterns. Rater-perceived excellence is related to the supervisor's focusing on the resident's immediate experiences and making many synthesizing comments in depth. The Psychotherapy Supervision Inventory can be used to orient supervisors to supervision and provide feedback about their behavior.*

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There has been little systematic research on psychotherapy supervision. Most reports of supervision are descriptions or studies of the process (1–11). Only a few used direct observational data of supervision, and these did not assess reliability adequately (12, 13). The Psychotherapy Supervisory Inventory (14) was developed to measure dimensions of the behavior of supervisors in videotaped supervision sessions. Categories of behavior were drawn from empirical observations of supervision and the therapeutic process (13–15). Previous research has established that trained observers can distinguish patterns of supervisory behavior with considerable agreement (14). The present study explores patterns of supervisory behavior using the Psychotherapy Supervision Inventory. A new variable was developed, the rater's perception of the excellence of the supervisor, to provide a measure of the supervisor's ability as a teacher and facilitator of resident learning during the videotaped session.

## METHOD

All psychotherapy supervisors at two departments of psychiatry were asked if their supervision sessions could be videotaped. Both the supervisors and residents involved were told that supervisory interaction would be assessed. Thirty-four (87%) of the 39 supervisors in the two departments participated in the study. All but three were psychiatrists; the three nonpsychiatrists were doctoral-level psychologists. Supervisors and trainees were well along in their supervisory relationship when the first supervision session was videotaped; the mean number of days from the time they were as-

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signed to meet on a weekly basis at the beginning of the academic year to the time of taping was 239.2 days (SD=72.4). Videotaping was not done in the regular meeting place for supervisor and resident; usually it was done in a television studio. Most supervisors were experienced. Twenty-eight (82%) had supervised 30 or more residents. Two (6%) had supervised about 20 residents. Only four (12%) were beginner supervisors, having supervised only three to four residents. Nineteen supervisors were videotaped with two different residents. In all, 53 videotapes were rated (one for each of the 34 supervisors plus one for each of 19 supervisors with a second resident). Fourteen residents in postgraduate year two, 25 in postgraduate year three, and 14 in postgraduate year four were videotaped. The mean number of days between videotaping with two different residents was 210.3 days (SD=197.3).

Videotapes were rated independently by all four of us using the Psychotherapy Supervision Inventory. We are experienced supervisors, having supervised a mean of 64.5 residents (SD=38.7, range=22–112) on an individual basis. Three of us had also taught psychotherapy seminars to residents before making these ratings. Only supervisory sessions in which the resident had an ongoing relationship with a patient were rated. We observed the complete session on each tape before making the ratings. The average of the four raters' scores for each scale was entered into the analysis.

The Psychotherapy Supervision Inventory has 13 scales that are described in more detail elsewhere (14). Seven of the scales measure the content of the supervisor's comments: 1) therapist focus, 2) patient focus, 3) frequency of intellectually oriented and discursive comments, 4) frequency of experientially oriented comments, 5) frequency of clarificatory and interpretative comments, 6) intensity of confronting statements, and 7) peak level of depth of exploration. Six scales measure interactions between the supervisor and therapist, relatively independent of content: 8) activity level of the supervisor, 9) dominance of the supervisor, 10) dominance of the therapist, 11) peak levels of comfort, 12) peak levels of tension, and 13) the amount of empathy of the supervisor with the therapist or the patient. Each variable is rated on a scale from 1 to 7 on which 1=little and 7=extremely high.

Intraclass correlation coefficients (ICC) (16–18) ranged from 0.22 to 0.62 and were significant for all scales (14). We used the ICC to compare the variance between raters with the variance within raters (16). The ICC is sensitive to skewness and would be low if there were little variance between raters (18). To address this problem, we adopted Finn's index (18), a measure comparing the variance within raters with the variance of ratings that would be predicted by random ratings. A higher value for Finn's index than for the ICC means that there was less variability in the ratings and more agreement between raters (18). Finn's index ranged from 0.52 to 0.85 (14).

A new variable, rater-perceived excellence of the supervisor, was constructed. This is a measure of the rater's global judgment of the supervisor as a teacher and facilitator of resident learning during the videotaped session. We rated our perceptions of each supervisor during an entire videotaped session on a scale from 1 to 7 on which 1=little quality and 7=extremely high quality. We each rated 15 of the 53 videotaped sessions while blind to each other's ratings. These ratings were used to compute the ICC (16–18) and Finn's index (18). The statistical significance of the ICC was tested by using analysis of variance (16). The reliability for the mean scores of two and four raters was tested by using the Spearman-Brown coefficient. This coefficient was interpreted to mean that if another random sample of raters were to rate the same subjects, the reliability coefficient would represent the correlation between the two sets of data (16, 19). Our ratings of the excellence of the supervisors were obtained for all of the videotaped sessions, and the averages of the four ratings of each session were entered in the data analysis. A correlation matrix of the Psychotherapy Supervision Inventory variables plus the rater-perceived excellence variable was constructed, and the Bonferroni correction for the effect of multiple correlations was applied to test the significance of the correlations (20).

Cluster analysis, a multivariate statistical procedure, was done to classify the scales of the Psychotherapy Supervision Inventory and the excellence variable into homogeneous groups (21, p. 165). After the only videotaped supervision session of 15 of the supervisors and the first session of 19 of the supervisors were analyzed, the scales and the excellence variable were subjected to a hierarchical agglomerative analysis that produced a tree diagram of the variables (22, pp. 35–45). In this procedure, the variables were grouped into larger and larger clusters until all the variables were members of a single group (21, p. 189). Distance or similarity between the variables was measured by the product-moment correlation coefficient, and the average linkage method was used for combining variables (22, p. 61). The data were subjected to iterative partitioning with a K-means procedure for the number of clusters observed on the tree diagram, a procedure that assigns supervisors to a cluster (22, pp. 45–47). The variables for the two groups defined by K-means analysis were compared by using two-tailed t tests.

The behavior patterns of each of 19 of the supervisors in a videotaped supervision session with one resident were compared with their behavior patterns in a session with another resident by using discriminant function analysis. This statistical procedure identifies variables that best distinguish the groups being compared (21, p. 75). In addition, the behavior patterns of all 34 supervisors with residents in three different years of training were compared by using discriminant function analysis.

In an effort to understand the determinants of our ratings of excellence of the supervisors, we entered this as a dependent variable and the Psychotherapy Supervision Inventory scale scores as independent variables in a stepwise multiple regression analysis. This statistical procedure identifies a subset of independent vari-

**TABLE 1. Correlations Between Psychotherapy Supervision Inventory Scores and Excellence Ratings of 34 Supervisors**

| | Correlation (r) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Item | Therapist Focus | Patient Focus | Intellectual Orientation | Experiential Orientation | Clarification and Interpretation | Confrontation | Depth | Activity |
| Psychotherapy Supervision Inventory scales | | | | | | | | |
| Patient focus | –0.79[a] | | | | | | | |
| Intellectual orientation | –0.44 | 0.41 | | | | | | |
| Experiential orientation | 0.79[a] | –0.63[b] | –0.75[a] | | | | | |
| Clarification and interpretation | 0.41 | –0.10 | –0.19 | 0.36 | | | | |
| Confrontation | 0.66[b] | –0.60[c] | –0.08 | 0.37 | 0.31 | | | |
| Depth | 0.81[a] | –0.56[c] | –0.44 | 0.70[a] | 0.49 | 0.53 | | |
| Activity | 0.31 | –0.21 | 0.26 | 0.11 | 0.55 | 0.22 | 0.15 | |
| Supervisor dominance | 0.50 | –0.29 | 0.10 | 0.29 | 0.62[b] | 0.41 | 0.42 | 0.84[a] |
| Therapist dominance | –0.39 | 0.19 | –0.09 | –0.25 | –0.57[c] | –0.34 | –0.30 | –0.76[a] |
| Comfort | 0.01 | 0.13 | –0.46 | 0.27 | 0.32 | –0.46 | 0.24 | –0.03 |
| Tension | 0.19 | –0.30 | 0.03 | 0.12 | –0.16 | 0.54 | 0.03 | 0.05 |
| Empathy | 0.70[a] | –0.52 | –0.51 | 0.74[a] | 0.68[d] | 0.43 | 0.78[a] | 0.26 |
| Perceived excellence | 0.76[a] | –0.51 | –0.53 | 0.78[a] | 0.65[b] | 0.40 | 0.76[a] | 0.28 |

[a] p<0.0001 with Bonferroni correction.
[b] p<0.01 with Bonferroni correction.
[c] p<0.05 with Bonferroni correction.
[d] p<0.001 with Bonferroni correction.

ables that best predict a dependent variable, taking into account the correlations among the variables (21, p. 9). This analysis was based on the only videotaped supervision session of 15 of the supervisors and the first session of 19 of the supervisors.

## RESULTS

The measure assessing the rater's perception of the excellence of the supervisor had a high degree of interrater reliability (ICC=0.62, p=0.0001); Finn's index was 0.79, indicating less variance in the ratings and considerable agreement between raters. Moreover, with r=0.77 for two raters and r=0.87 for four raters, considerable agreement among two and four raters was found. Table 1 provides the correlation matrix of all the variables.

Cluster analysis of the 34 different supervisors resulted in a tree diagram depicting two clusters of variables at the highest level of organization (figure 1). K-means analysis for the two clusters assigned 25 supervisors to one group and nine supervisors to the other. The cluster of 25 contained supervisors who were empathic and judged to be relatively excellent in their facilitation of resident learning, who focused their comments on the trainee and somewhat more on the patient, who made many clarifications (both experiential and intellectual) in some depth, who were somewhat confronting, and who dominated the interaction but not to the exclusion of the resident's involvement. The cluster of nine included supervisors rated lower in empathy and in the degree they were perceived to facilitate resident learning. These supervisors focused more on the patient and less on the therapist and made mostly intellectual and discursive comments to the near exclusion of entering into the resident's immediate experiences. They made some clarificatory comments but were not at all confrontative or clearly in charge of the supervision. All four beginner supervisors were in this second group. Three of the supervisors in this group, however, had considerable supervision experience, having supervised more than 30 residents each.

A comparison of the two groups on each variable using two-tailed t tests revealed no significant differences on the activity, comfort, or tension variables (table 2).

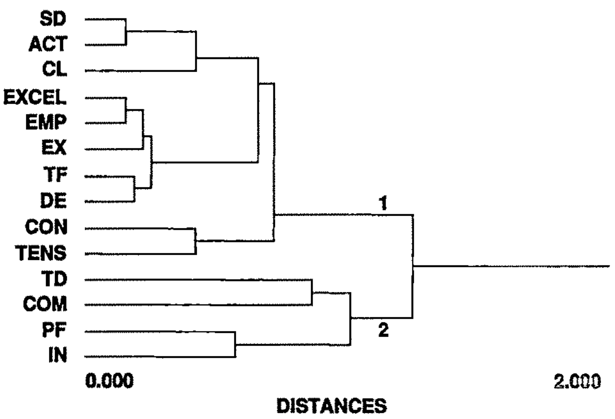
Discriminant function analyses revealed no distinguishing variables between the two sessions of the 19 supervisors who had sessions with two different residents videotaped. These analyses also revealed no distinguishing variables between supervisors of residents in different years of training. Multivariate F statistics for Wilks's lambda were not significant for these two comparisons (lambda=0.51, F=1.5, df=14, 23, p<0.16, and lambda=0.77, F=0.82, df=14, 38, p<0.65, respectively).

Stepwise multiple regression analysis of the 34 supervisors revealed that for the rater's perception of excellence (the dependent variable), empathy accounted for 72% of the variance (standardized coefficient=0.63, p<0.0001) and focus on the therapist accounted for 77% of the variance (standardized coefficient=0.32, p<0.01) (F=52.18, df=2, 31, p<0.0001). In this analysis, empathy is a global indicator. Therefore, in order to look at the relationship of the raters' judgments about supervisors' excellence as teachers to more discrete patterns of supervisory behavior, empathy was dropped from the regression equation. When this was done, experiential orientation accounted for 60% of the variance of the rater-perceived excellence variable (standardized coefficient=0.46, p<0.0001), clarification and interpretation accounted for 76% of the variance (standardized coefficient=0.35, p<0.001), and depth accounted for 79% of the variance (standardized coefficient=0.27, p<0.04) (F=38.41, df=3, 30, p<0.0001).

TABLE 1 (continued)

| Correlation (r) | | | | |
|---|---|---|---|---|
| Supervisor Dominance | Therapist Dominance | Comfort | Tension | Empathy |
| | | | | |
| –0.87[a] | | | | |
| –0.02 | 0.06 | | | |
| 0.05 | –0.11 | –0.80[a] | | |
| 0.45 | –0.30 | 0.40 | –0.12 | |
| 0.42 | –0.35 | 0.38 | –0.10 | 0.85[a] |

FIGURE 1. Cluster Analysis of Excellence Ratings and Psychotherapy Supervision Inventory Scores of 34 Psychotherapy Supervisors[a]



[a]EXCEL=rater-perceived excellence. Psychotherapy Supervision Inventory scales: SD=supervisor dominance, ACT=activity, CL=clarification and interpretation, EMP=empathy, EX=experiential orientation, TF=therapist focus, DE=depth, CON=confrontation, TENS=tension, TD=therapist dominance, COM=comfort, PF=patient focus, and IN=intellectual orientation.

## DISCUSSION

Within the context of an established supervisory relationship, the behavior of psychotherapy supervisors appeared not to change significantly with different psychiatry residents or across different years of resident training. These findings provide support for earlier observations of enduring and consistent styles of psychotherapy supervisors (13). About three-quarters of this group of 34 supervisors were judged to be at the higher end of excellence in facilitating resident learning and were rated higher in empathy. These supervisors provided a mix of comments directed to the therapist and the patient on intellectual as well as experiential levels and made many synthesizing comments in some depth. In contrast, one-quarter of the supervisors were rated low in the degree to which they facilitated resident learning and in empathy. Their comments were more often discursive, intellectualized statements and generalized elaborations of the material, with little attention to the specific concerns of the student. Of note, four of the nine supervisors with low ratings were inexperienced beginners, but three were senior supervisors who had supervised many residents.

The supervisors' activity levels, as well as levels of tension and comfort in the session, were not distinctive aspects of supervision when considered within the context of all other variables. In other words, the amount of talking done by supervisors was a trait that appeared to have little to do with perceptions of teacher excellence or empathy. Similarly, levels of tension and comfort had an ebb and flow in any supervision session and appeared not to have a bearing on judgments about excellence and empathy.

This research is an effort to systematize the study of supervision. Raters showed notable agreement in discerning the behavior of supervisors and in their overall judgments as to the excellence of the supervisors' facilitation of residents' learning. Our findings are in general agreement with the supervision literature as well as the current understanding of the clinical teaching process (8–11, 23, 24). Supervisors judged to be excellent were empathic and focused on the immediate concerns of the trainee. They had an experiential orientation and tailored their comments to the residents' concerns. Such supervisors emphasized the patient's or the therapist's thoughts and feelings as closely as possible to the way they were actually elaborated and stayed with the immediate material, including cognitive and affective elements. Furthermore, these supervisors frequently synthesized and reframed material for the resident and made comments in depth. They were teachers who reflected with residents on their actions as therapists and supervisees (8, 25).

There are limitations to this research. First, we studied supervisors as they appeared on videotapes. What patterns of behavior changed as a result of being videotaped is unclear. The literature on observed psychotherapy and interviews does not provide a clear guide to what specifically changes as a result of the observation process. Therapists are often conscious of being observed and experience varying levels of anxiety about the possibility of criticism from peers as to their competence. However, fulfilling the task at hand prevails, in spite of these concerns (26–33). We found relative stability of the patterns of behavior of supervisors with two different residents as measured by the Psychotherapy Supervision Inventory scales even after a considerable lapse of time between taped sessions. It is possible that some patterns of behavior could have changed consistently across sessions in response to taping, but there is no information about this. Asking residents and supervisors about this would provide a sense of which

**TABLE 2. Psychotherapy Supervision Inventory Scores and Excellence Ratings of 34 Supervisors Divided Into Two Groups by K-Means Analysis[a]**

| | Group 1 (N=25) | | Group 2 (N=9) | | |
|---|---|---|---|---|---|
| Item | Mean | SD | Mean | SD | t (df=32) |
| Psychotherapy Supervision Inventory Scale | | | | | |
| Therapist focus | 4.51 | 1.10 | 2.03 | 0.38 | 48.83[b] |
| Patient focus | 5.04 | 0.74 | 6.14 | 0.29 | 25.45[b] |
| Intellectual orientation | 4.63 | 1.18 | 5.58 | 0.69 | 4.41[c] |
| Experiential orientation | 4.53 | 1.10 | 2.39 | 0.83 | 24.82[b] |
| Clarification and interpretation | 5.00 | 1.05 | 3.44 | 1.07 | 9.88[d] |
| Confrontation | 3.58 | 1.47 | 1.97 | 0.77 | 14.54[e] |
| Depth | 4.58 | 1.02 | 2.75 | 0.62 | 19.88[b] |
| Activity | 4.84 | 0.98 | 4.03 | 1.27 | 3.83 |
| Supervisor dominance | 5.46 | 0.78 | 4.25 | 1.31 | 8.98[d] |
| Therapist dominance | 3.28 | 0.71 | 4.06 | 1.16 | 5.12[c] |
| Comfort | 4.54 | 1.09 | 3.92 | 0.99 | 0.02 |
| Tension | 4.09 | 1.21 | 4.39 | 1.17 | 0.69 |
| Empathy | 5.26 | 0.68 | 3.11 | 0.66 | 32.30[b] |
| Perceived excellence | 4.66 | 0.85 | 2.33 | 0.63 | 44.53[b] |

[a] Group 1 included supervisors who were rated as empathic and relatively excellent in their facilitation of resident learning, as focusing their comments on the trainee and somewhat more on the patient, as making many clarifications in some depth, as somewhat confronting, and as dominating the interaction but not to the exclusion of the resident's involvement. Group 2 included supervisors who were rated as lower in empathy and in the degree they were perceived to facilitate resident learning, as focusing more on the patient and less on the therapist, as making mostly intellectual and discursive comments to the near exclusion of entering into the resident's immediate experiences, as making some clarificatory comments, and as not at all confrontative or clearly in charge of the supervision.

[b] $p<0.0001$.

[c] $p<0.05$.

[d] $p<0.01$.

[e] $p<0.001$.

patterns of behavior, if any, changed while taping. This question merits study.

A second limitation of this study is that ratings were based on experts' judgments of the supervisor without attention to the supervisors' or supervisees' perspectives. Knowledge of these perspectives would provide data about the transfer of learning from the supervisory session to the resident's interaction with the patient. This item also merits exploration.

Finally, a third limitation of this study is that the raters' judgments of excellence reflected their biases, likely based on a tacitly agreed upon model of teaching psychotherapy. Although the findings appear to fit with what is known about the supervisory process, they merit validation from other researchers informed about supervision who also observe videotaped sessions and rate a large number of such sessions in a systematic fashion.

How can the findings of the present study be used in psychotherapy education? The Psychotherapy Supervision Inventory can be used to orient supervisors to styles of supervision and to provide feedback about their individual patterns of behavior. Training can be done individually or in a group. Group training of supervisors has been shown to improve resident ratings of supervision (12). Such training is best done by teachers who are informed about the supervisory process by having reviewed and discussed observed supervision sessions.

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# An Outcome Study of Psychotherapy for Patients With Borderline Personality Disorder

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*Objective: This study evaluated the effectiveness of well-defined outpatient psychotherapy for patients with borderline personality disorder. Method: Thirty patients with borderline personality disorder diagnosed according to the* DSM-III *criteria were given twice weekly outpatient psychotherapy for 12 months by trainee therapists who were closely supervised. The treatment approach was based on a psychology of self (this term being used in its broad sense), and strong efforts were made to ensure that all therapists adhered to the treatment model. Outcome measures included frequency of use of drugs (both prescribed and illegal), number of visits to medical professionals, number of episodes of violence and self-harm, time away from work, number of hospital admissions, time spent as an inpatient, score on a self-report index of symptoms, and number of* DSM-III *criteria (weighted for frequency, severity, and duration) fulfilled. Results: The subjects showed statistically significant improvement from the initial assessment to the end of the year of follow-up on every measure. Moreover, 30% of the subjects no longer fulfilled the* DSM-III *criteria for borderline personality disorder. This improvement had persisted 1 year after the cessation of therapy. Conclusions: The results suggest that a specific form of psychotherapy is of benefit for patients with borderline personality disorder.*

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Until comparatively recently, no treatment was available for persons with severe personality disorder. Individuals so badly damaged were considered "unanalyzable." However, over the last two decades, methods of treating borderline and narcissistic personalities have been steadily evolving. The aim of this project was to evaluate the effectiveness of an identifiable form of psychotherapy, conducted by trainee therapists working under close supervision, in the management of outpatients with borderline personality disorder. As far as we are aware, this report describes the first prospective study of this kind.

## THE STUDY

A group of patients with severe personality disorder were given psychotherapy for 12 months, at two sessions per week. Measures were taken to assess the patients before, during, and after treatment.

### *Treatment Model*

We made considerable efforts to develop a coherent, consistently applied, and identifiable treatment approach. It was based on the notion that borderline personality disorder is a consequence of a disruption in the development of the self. The principal assumption is that a certain kind of mental activity, found in reverie and underlying symbolic play, is necessary to the generation of the self. This kind of mental activity is nonlinear, associative, and affect laden. In early life its presence depends on a sense of "union" with caregivers, in which they are experienced as extensions of the developing individual's subjective life (1, p. 243). Development is disrupted through repeated "impingements" (2) of the social environment, which have an impact on the child rather like that of a loud noise. This effect arises through actual stimuli (abuse of various kinds is common in the early lives of borderline patients [3–5]), through high anxiety, and through responses that do not connect with the child's immediate reality and so seem to come from "outside."

The aim of therapy is maturational. Specifically, it is to help the patient discover, elaborate, and represent a personal reality (6), i.e., a reality that relates to an inner life

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and that has an affective core (7). The first task is to establish the enabling atmosphere in which the generative mental activity can arise. In order to do so, the therapist must imaginatively immerse himself or herself in the embryonic inner life of the patient. Empathy, however, inevitably fails. The second main task of the therapist is to detect these failures, to focus with the patient on his or her experience at the moment of the failures, and then to allow these experiences to be the starting point of experiential explorations. Such empathic failures, or disjunctions, are indicated by 1) negative affect (e.g., deadness, anxiety), 2) linear thinking, 3) an orientation toward events and the outer world, 4) a change in self state (e.g., devaluing, grandiose), and 5) emergence of transference phenomena (8). An illustrative therapy session, which includes a further description of the treatment method, is reproduced elsewhere (9).

This therapeutic approach was influenced by Robert Hobson's work with borderline patients at the Bethlehem Royal Hospital, London, during the 1960s (10). The theoretical framework includes essential elements from the work of Kohut (11) and Winnicott (12). The model is consistent with Pine's description of the "borderline-child-to-be" (13).

Whether therapists adhere to the therapeutic model is a major problem in psychotherapy outcome research. In this project, the problem was approached in three main ways. First, all therapists were given instruction in the method by means of weekly seminars. Second, all therapy sessions were audiotaped and replayed with a supervisor once a week. In this way, the supervisor could make judgments about adherence to the model and suggest alterations of therapists' behavior. Third, in order to achieve maximum uniformity of approach, supervisors, on occasion, supervised together.

Ideally, a manual that defines therapeutic behavior is used to establish adherence, in the manner of Luborsky (14). This might be done by independent judges rating transcripts, which facilitates replication studies and also matching of outcome against the treatment model. However, in this case such a process is complex, since the therapeutic field is "intersubjective" (15). The therapeutic response cannot be judged as "correct" before it is made. Its suitability is evident only after it has been made. For example, a patient who had spent much of his early life in an orphanage and who could not remember anything before the age of 10 began a session by announcing that his girlfriend was pregnant. This appeared to be "no problem," since she would get an abortion. After a few connecting sentences, the patient, showing little affect, went on to say that he wondered whether some early memories were beginning to be recovered, since he had had "images" of himself as a terrified child being dragged from under a bed, presumably to be taken to the orphanage. The therapist then remarked that the forthcoming abortion seemed to have triggered feelings relating to his being "gotten rid of" by his own mother. The patient said, "Good point," in a rather pompous voice. He then recounted, without any apparent reason, successive incidents in which he had been physically attacked and injured; had been humiliated after revelation of an emotional state; had felt "paranoid"; and had been enraged. A disjunction was signaled by the change from inner concerns ("images") to outer events, by the affect which escalated from agitation to anger, and by the alteration in self state indicated by the pompous voice. It is apparent that the therapist's response was sensed as an intrusion (16). In one sense it was "correct," in that it was accurate; in another it was not, since it produced a disjunction. The "correct" subsequent response is to explore the effect of the first response. This requires skill, since it may be sensed as a second intrusion.

A second difficulty in rating transcripts is that the nuances of the interchange are often reflected in changes in voice, which are a matter of subjective judgment. In the incident just described, for example, the change of voice at "Good point" was not noticed by the therapist.

Despite these problems, a linguistic analysis of transcripts, based on Halliday's systemic grammar (17), is underway in order to provide data for a future manual that will address a limited range of therapeutic issues.

### *Subjects*

Patients were referred by psychiatrists, allied health professionals, community clinics, and inpatient units, and some were self-referred. Eighty-five consecutive patients were rated by three independent psychiatrists according to the *DSM-III* criteria for borderline personality disorder in a diagnostic interview that included the Diagnostic Interview for Borderline Patients (18). They were then seen by a consultant psychotherapist who made a diagnosis of borderline personality disorder on dynamic grounds. Potential subjects were also required to display persisting social dysfunction (e.g., unemployment for more than 12 months, absence of or severely dysfunctional interpersonal relationships, antisocial behavior). Sixty-seven patients fulfilled these criteria. All 67 had previously been unsuccessfully involved in other forms of therapy for a period of not less than 6 months.

Eight of these patients were considered unsuitable for psychotherapy for the following reasons: borderline intellectual retardation (N=2), language difficulty (N=2), antisocial and uncontrollable violent behavior (N=1), and failure to keep three consecutive appointments (N=3). Fifty-nine potential subjects now remained.

After the course of treatment was explained, 11 patients declined treatment or accepted but failed to keep further appointments. At this stage written consent was obtained from the remaining 48 patients, all initial assessments were performed, an appointment was made for an interview with a close friend or relative of each patient, and the patient was assigned to a therapist. After 6 months of therapy and at the conclusion of therapy, further assessments were performed. During the 12 months, eight patients dropped out of therapy, mostly in the first 3 months, before a firm relationship had been established with the therapist. This left 40 patients who completed 12 months of therapy. (Seven of these elected to continue therapy for a longer time and so were excluded from the present study. They were doing well. The decision to omit them was on the grounds that they had not terminated and that their current state might seem to inflate the value of the treatment.) It was explained to the 33 patients who completed the 12-month course of therapy that they would be contacted a year later "to see how they were doing." Of these 33 patients, three could not be contacted. Thus, of the 48 patients who accepted therapy, 37 completed all assessments. Seven continued therapy and were excluded from the present study. The remaining 30 patients are the subject of this article.

### *Therapists and Supervisors*

The 20 therapists were relatively untrained in psychotherapy, since they were trainee psychiatrists (1–3 years of psychiatry training, 1–2 years of postgraduate medical training), registered nurses, and psychologists. They were young (average age=30.6 years—close to the average age of the patients), 12 were single and eight were married, and 11 were male and nine female. Six had postgraduate qualifications.

Although the supervisors had different training experiences, they developed fairly consistent supervisory behavior. Two were trained by Robert Hobson, a third was a psychoanalyst trained in London, a fourth was oriented toward Sullivan's interpersonal psychology, and two others were oriented toward Kohut's self psychology.

## METHOD

Demographic data—age, sex, occupation, partner's occupation, marital status, education, physical health, place of residence, parent's or surrogate parent's occupation, and country of origin—were collected on all subjects. (A large number of patients had been adopted, placed in foster homes, or institutionalized early in life.)

The number of *DSM-III* criteria for borderline personality disorder fulfilled by the subject was determined. Each was weighted on the basis of frequency, severity, and duration, and the total score was recorded. (A number of patients also fulfilled the *DSM-III* criteria for other personality disorders, such as schizotypal, histrionic, narcissistic, and antisocial.) No modifications were made following publication of *DSM-III-R*, since the criteria were essentially unchanged.

The Cornell Index (19) provided a self-report rating of symptoms. An initial measure was taken to assess severity of dysfunction and as a baseline for later comparison. This index is generally used for quite disabled patients. Consequently, it was considered more suitable for our population of subjects than instruments used for neurotic patients. Measures were taken at the initial assessment, after 6 months of therapy, after 12 months of therapy, and at follow-up 12 months later.

Objective behavioral measures were collected en bloc for the entire year preceding and for the year following therapy. They included amount of time away from work (in months), use of medical facilities (number of outpatient visits to a medical facility each month), quantity of drugs (prescribed and illegal) used on a daily basis, self-destructive behavior and outwardly directed violence (number of episodes over a 12-month period), and number of hospital admissions and time spent as an inpatient (in months). Information was obtained from the patient, friends or relatives, medical records, and referral sources. Such methodology reduces errors that may be inherent in the patient's own report. All assessments were performed by the research psychiatrist (J.S.), who was not involved in the therapy process.

The MINITAB data analysis software was used to analyze results. Paired t tests were used to explore the differences between the independent variables before and after therapy, followed by post hoc Bonferroni adjustments of alpha levels.

## RESULTS

The mean age of the subjects was 29.4 years (SD=7.9). Nineteen were female and 11 male. Nine were married. Only three had not completed junior high school; six had undertaken college studies. Eight subjects had received long-term institutional or foster care. None had serious medical problems. Twenty-two (73.3%) were receiving government financial assistance (sickness benefits, invalid pension, unemployment benefits, etc.). The remaining eight worked erratically in various nonskilled (N=2), skilled (N=3), and professional (N=3) occupations. Only two owned their own homes; the remainder were renting privately, living with friends or relatives, or in government housing.

There was a significant reduction in the number of *DSM-III* criteria fulfilled at follow-up (mean=10.50) compared with pretreatment (mean=17.40) (table 1). The most frequently observed changes were reductions in impulsivity, affective instability, anger, and suicidal behavior. It is also noteworthy that at follow-up, only 70% (N=21) of the 30 subjects fulfilled the *DSM-III* criteria for borderline personality disorder, compared with 100% before treatment.

There was a marked and statistically significant improvement on all seven objective behavioral measures over the 12 months following therapy compared with the 12 months before therapy when pretreatment scores were compared with follow-up scores (table 1); for example, medical office visits dropped to only one-seventh of pretreatment rates (3.50 to 0.47 per patient per month), and self-harm and drug use dropped to one-fourth of pretreatment rates.

Cornell Index scores had dropped significantly 12 months after treatment when compared with pretreatment levels (table 1); the rate of change over the 2 years was approximately linear (mean scores at 0, 6, 12, and 24 months were 42.63, 41.00, 33.60, and 28.63).

**TABLE 1. Scores of 30 Patients on Behavioral Measures, the Cornell Index, and *DSM-III* Criteria for Borderline Personality Disorder for the 12 Months Preceding and Following Psychotherapy**

| Measure | One Year Before Therapy Mean | One Year Before Therapy SD | One Year After Therapy Mean | One Year After Therapy SD | Paired t Test t (df=29) | Paired t Test p |
|---|---|---|---|---|---|---|
| Violent behavior (episodes per year) | 2.70 | 4.05 | 0.80 | 1.80 | 3.69 | <0.001 |
| Drugs used (number per day) | 3.80 | 3.42 | 0.63 | 0.80 | 5.05 | <0.001 |
| Medical visits (number per month) | 3.50 | 2.75 | 0.47 | 0.57 | 6.16 | <0.001 |
| Self-harm (episodes per year) | 3.77 | 4.66 | 0.83 | 1.18 | 3.82 | <0.001 |
| Time away from work (months per year) | 4.47 | 4.10 | 1.37 | 2.57 | 4.90 | <0.001 |
| Hospital admissions (number per year) | 1.77 | 1.52 | 0.73 | 1.02 | 3.03 | <0.01 |
| Time as an inpatient (months per year) | 2.87 | 2.33 | 1.47 | 1.87 | 2.73 | <0.05 |
| Cornell Index[a] score (at end of year) | 42.63 | 14.90 | 28.63 | 13.35 | 5.68 | <0.001 |
| *DSM-III* score[b] (at end of year) | 17.40 | 2.87 | 10.50 | 5.08 | 7.48 | <0.001 |

[a] A self-report rating of symptoms.
[b] Number of criteria for borderline personality disorder (weighted for frequency, severity, and duration) fulfilled by subject.

## DISCUSSION

Thirty patients with the diagnosis of borderline personality disorder were treated for 12 months. They showed significant symptomatic and behavioral improvement. Moreover, 30% no longer fulfilled the *DSM-III* criteria for borderline personality disorder. Improvement was maintained at follow-up 12 months later. These findings suggest that a specific form of therapy, supervised in a focused and coherent way, is helpful to a group of people who, most studies report, "do not fare well at follow-up" (20).

Studies of the management of borderline personality disorder have been criticized on the grounds that diagnostic criteria are not clear, outcome measures are relatively subjective, designs are retrospective rather than prospective, and there are no control measures (21). In this study we attempted to overcome these problems. The patients were carefully diagnosed according to *DSM-III,* the outcome measures were objective, and the study was prospective. The principal difficulty, however, concerned the method of control; we used control measures rather than control subjects.

No sensible or ethical solution to the problem of control subjects was evident to us. Ideally, a "placebo" therapy would be compared with the treatment model, in the manner of pharmacotherapy studies. The control subjects would spend the same amount of time as the other patients in sessions with a therapist. The therapist, however, blind to these circumstances, would be instructed by a supervisor to make interventions likely to have no therapeutic effect. Such a design seemed unacceptable from several points of view, including the communal. The clinic is the only one of its kind. The expectation of referral sources was that their patients, who had usually already received extensive and various treatments including drugs and ECT, would receive a "different" therapy, specially geared toward patients with severe personality disorders. Attempts to assign patients to treatments they had previously encountered resulted in these patients' dropping out. An alternative, the use of patients on the waiting list as control subjects, is impracticable with such an unstable population. On the other hand, since personality disorder is relatively enduring, comparisons between different periods of the patients' lives offer a suitable means of obtaining a control. Thus, 1 year of the patients' lives before treatment was compared with 1 year after.

This study cannot be compared with most others in this area, since they usually concern inpatients and are retrospective. Tucker et al. (20), however, reported on a prospective study of inpatients, the results of which, over 2 years, were favorable.

Of particular interest in the present study is the finding that patients were able to terminate treatment and maintain their improvement. Alternative explanations for the good outcome did not seem plausible. Those that were considered included spontaneous remission, a ceiling effect, selective attrition, and intercurrent therapy.

Spontaneous remission seemed an unlikely explanation for the results. In a previous study of psychotherapy outcome, a period of 6 months with continuous symptoms was used to differentiate patients with chronic illness from those whose illness remitted (H. Brodaty, unpublished doctoral thesis, 1985). All patients in our trial had continuous symptoms for 12 months, the majority for many years.

A second possible explanation for the improvement of our patients might be a so-called ceiling effect. Put another way, were the patients so disturbed that they could deteriorate no further? The histories of our patients did not support this possibility. For example, many had had inpatient treatment, but no patient entered the trial at one of these periods of crisis.

The possibility that selective patient attrition distorted the results of this study was not supported. There was no evidence that the more disturbed patients had dropped out. Comparisons were made between trial subjects and dropouts on demographic data (age, sex, occupation, social class, etc.), Cornell Index scores, fulfillment of *DSM-III* criteria, and behavioral measures. No significant differences were found on any measure. There was a tendency for the dropouts to live farther from the treatment center, although this difference did not reach statistical significance. Furthermore, the dropout rate was low—16%—compared with the rates in previous studies (22, 23).

Finally, any intercurrent treatments were carefully monitored in this study. On entering the trial, all patients had their medications gradually withdrawn. Hypnotics and minor tranquilizers were given to a minority of patients on occasion and to patients who needed hospitalization. Those few patients who needed hospital admission during therapy, usually during a crisis, continued to receive psychotherapy, while the ward provided a supportive, containing environment, but no other "treatment" was given. At each assessment interview interviewers asked about intercurrent treatment, appointments with other doctors, and alternative therapies. Little evidence of these was found. One patient who continued to see a previous therapist and who received medications from him eventually dropped out. Most patients had more or less exhausted other treatment options before referral into our trial.

In conclusion, this report suggests that a specific form of psychotherapy is of benefit for borderline patients. All patients will be followed up at 5 and 10 years. The cost effectiveness of treatment and aspects of the therapeutic process that are related to change are the basis for subsequent reports.

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# Differential Response of Seven Subjects With Autistic Disorder to Clomipramine and Desipramine

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*Objective:* *Clomipramine, a serotonin reuptake blocker that has unique antiobsessional properties, was hypothesized to have a different effect from that of desipramine, a tricyclic antidepressant with selective adrenergic effects, for the stereotyped, repetitive behaviors in autism.* *Method:* *Seven subjects, ages 6–18 years, with autistic disorder completed a 10-week double-blind, crossover trial of clomipramine and desipramine following a 2-week single-blind, placebo phase.* *Results:* *Clomipramine was superior to desipramine and placebo, as indicated by standardized ratings of autism and anger as well as ratings of repetitive and compulsive behaviors. Clomipramine and desipramine were equally superior to placebo for ratings of hyperactivity. Parents of all seven subjects elected to have their children continue to take clomipramine after the study.* *Conclusions:* *Clomipramine and desipramine are differentially effective in treating the obsessive-compulsive and core symptoms in autistic disorder. Biological links between compulsions and stereotyped, repetitive behaviors in autistic disorder should be explored.*

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Autistic disorder is a pervasive developmental disorder characterized by impairments in reciprocal social interaction, communication skills, and imaginative activity (*DSM-III-R*, pp. 33–39). Since Kanner's classic description (1), repetitive, stereotyped, and ritualistic behaviors have been considered an integral part of the syndrome. Ritualized body movements, repeated touching and sniffing of objects, ritualistic ordering, checking, and collecting, and insistence on precisely following routines are commonly present. Neurochemical investigation has consistently revealed elevated levels of whole blood or platelet serotonin in more than 25% of autistic subjects (2).

Clomipramine, a tricyclic antidepressant with potent serotonin reuptake blocking action, has been shown to be more effective than desipramine, a primarily noradrenergic agent, in treating obsessive-compulsive disorder (3) as well as unwanted repetitive behaviors such as trichotillomania (hair pulling) (4) and onychophagia (nail biting) (5). These studies raise the question of what additional abnormal ritualistic behaviors may be responsive to clomipramine. We hypothesized that the compulsive and stereotyped behaviors seen in autism would be differentially responsive to clomipramine relative to desipramine.

## METHOD

Seven subjects (five male and two female), between 6 and 18 years of age (mean=9.6 years, SD=4.4), who fulfilled the *DSM-III-R* and Autism Diagnostic Interview (6) criteria for autistic disorder were obtained through self-referral and referral by health care professionals. The severity of mental retardation and obsessive-compulsive symptoms for each subject is shown in table 1. All of the subjects were free of significant medical problems, including seizures, by history and by physical examination, and no subject's autism had a diagnosed organic cause. The subjects had been free of psychoactive medications for at least 3 months before the study. The study was approved by the National Institute of Mental Health (NIMH) institutional review board. Informed consent was obtained from the parents of all of the subjects before the start of the study, and the subject's assent was obtained when possible, depending upon his or her intellectual level.

The subjects underwent a 10-week double-blind, randomized, crossover trial of clomipramine (mean dose at week 5, 129 mg/day [SD=39], or 4.3 mg/kg/day [SD=0.8]) and desipramine (mean dose at week 5, 111 mg/day [SD=40], or 3.8 mg/kg/day [SD=1.2]) following a 2-week single-blind, placebo phase. Randomization was per-

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**TABLE 1. Clinical Characteristics of Seven Autistic Subjects in a Comparison of Clomipramine and Desipramine Treatment**

| Subject | Age (years) | Sex | Mental Retardation[a] | Obsessive-Compulsive Symptoms[b] |
|---|---|---|---|---|
| 1 | 6 | M | Mild | Mild |
| 2 | 6 | M | Moderate | Moderate |
| 3 | 6 | M | Moderate | Mild |
| 4 | 9 | F | Severe | Severe |
| 5 | 10 | F | Borderline | Severe |
| 6 | 12 | M | Severe | Moderate |
| 7 | 18 | M | Borderline | Severe |

[a] Clinical estimate of IQ: severe retardation=20–34, moderate=35–49, mild=50–70, borderline=71–84.

[b] Measured by a modified version of the NIMH Global Obsessive-Compulsive Scale (11).

formed by the National Institutes of Health pharmacy with a random number table. All medication was administered orally by parents twice a day. The initial dose was 25 mg/day, and the dose was increased every 4–5 days until positive effects or side effects were noted or a maximum of 250 mg/day, or 5 mg/kg/day, was reached. The maximum dose was usually reached between weeks 2 and 3, so that the subjects were maintained on their maximum doses for 2–3 weeks. After 5 weeks, the first-phase medicine was tapered over approximately 1 week concurrent with a gradual increase of the second-phase medicine, which was also given for 5 weeks. Plasma drug levels were ascertained during week 5 of each medication phase by high-performance liquid chromatography.

Weekly physician ratings included the Children's Psychiatric Rating Scale (7), the Clinical Global Impression (CGI) (8), a modified version of the obsessive-compulsive subscale of the Comprehensive Psychopathological Rating Scale (9), a modified version of the NIMH Obsessive-Compulsive Rating Scale (10), and modified versions of the NIMH Global Obsessive-Compulsive and Anxiety scales (11). The obsessive-compulsive rating scales were modified to make them more relevant for relatively nonverbal subjects. Intraclass correlation coefficients for two physicians who independently rated 10 autistic subjects from a separate sample with the modified obsessive-compulsive rating scales were 0.72 for the obsessive-compulsive subscale of the Comprehensive Psychopathological Rating Scale, 0.88 for the NIMH Obsessive-Compulsive Rating Scale, 0.94 for the NIMH Global Obsessive-Compulsive Scale, and 0.67 for the NIMH Global Anxiety Scale. Data were analyzed by repeated measures analysis of variance, with Bonferroni-corrected post hoc t tests (two-tailed), comparing ratings for baseline, placebo, week 5 of clomipramine treatment, and week 5 of desipramine treatment.

## RESULTS

Two subjects discontinued taking desipramine after 3 weeks during the second phase because of uncharacteristic and severe irritability and temper outbursts. For these subjects, ratings for week 3 of desipramine treatment were analyzed in place of week 5 ratings.

Clomipramine had a selectively beneficial effect, as measured by the 14-item autism-relevant subscale of the Children's Psychiatric Rating Scale (table 2). These 14 items have been found to represent four factors: autism (individual items measure withdrawal, rhythmic motions, abnormal object relations, unspontaneous relation to the examiner, and underproductive speech), anger/uncooperativeness, speech deviance, and hyperactivity (12). The percent change from baseline scores for each of these factors during placebo, week 5 of clomipramine, and week 5 of desipramine is shown in figure 1. Statistically significant improvement in the autism and anger factors and a trend toward improvement in the speech deviance factor were seen. For hyperactivity, both drugs were rated superior to placebo but not significantly different from each other.

As predicted, there was significant improvement in obsessive-compulsive symptoms with clomipramine but not desipramine, as measured by the modified NIMH Obsessive-Compulsive Rating Scale (table 2). All of these results contributed to the substantial superiority of clomipramine on the efficacy index of the CGI ($F=42.98$, $df=2, 12$, $p=0.0001$).

Additional ratings (modified obsessive-compulsive subscale of the Comprehensive Psychopathological Rating Scale and modified NIMH Global Obsessive-Compulsive and Anxiety scales) all showed significant ($p<0.05$, two-tailed t tests) improvement during clomipramine treatment as compared to baseline, placebo, and desipramine. The superiority of clomipramine over desipramine was not an artifact of behavioral deterioration when subjects were taking desipramine. No measure showed significant worsening in the desipramine phase as compared to baseline or placebo.

For the most part, side effects were minor and did not differ significantly between drugs. They included mild sleep disturbance, dry mouth, constipation, and, in one subject, a mild tremor when taking clomipramine. There were no serious cardiac or CNS side effects. As previously noted, two subjects discontinued desipramine after 3 weeks because of adverse behavioral effects.

As expected, plasma drug levels varied widely; at week 5, the mean clomipramine level was 159 ng/ml (range=56–301), the mean desmethylclomipramine level was 345 ng/ml (range=182–448), and the mean desipramine level was 325 ng/ml (range=75–291, except that one subject had a level of 839 ng/ml). There was no significant correlation between plasma drug levels and clinical ratings or side effects. (The subject with the desipramine level of 839 ng/ml had no side effects.)

The parents of all seven subjects elected, before the blind was broken, to have their children continue to take clomipramine after the study.

## DISCUSSION

This was the first controlled trial of a serotonin reuptake blocking agent for autistic disorder. In this double-blind comparison, clomipramine, a potent serotonin re-

**TABLE 2. Scores of Seven Autistic Subjects on the Children's Psychiatric Rating Scale[a] and a Modified Version of the NIMH Obsessive-Compulsive Rating Scale in a Comparison of Clomipramine and Desipramine Treatment**

| | Children's Psychiatric Rating Scale Score | | | | NIMH Obsessive-Compulsive Rating Scale Score | | | |
|---|---|---|---|---|---|---|---|---|
| Subject | Baseline | Placebo | Clomipramine[b] | Desipramine[b] | Baseline | Placebo | Clomipramine[b] | Desipramine[b] |
| 1 | 44 | 44 | 21 | 48 | 10 | 10 | 0 | 11 |
| 2 | 37 | 45 | 23 | 31 | 12 | 11 | 1 | 16 |
| 3 | 39 | 50 | 35 | 43[c] | 9 | 10 | 7 | 14[c] |
| 4 | 45 | 46 | 30 | 41[c] | 25 | 25 | 0 | 14[c] |
| 5 | 40 | 40 | 20 | 29 | 23 | 28 | 13 | 18 |
| 6 | 40 | 43 | 24 | 45 | 14 | 14 | 2 | 18 |
| 7 | 49 | 52 | 13 | 50 | 40 | 40 | 29 | 38 |
| Total group | | | | | | | | |
| Mean | 42 | 46 | 24[d] | 41 | 19 | 20 | 7[e] | 18 |
| SD | 4 | 4 | 7 | 8 | 11 | 12 | 11 | 9 |

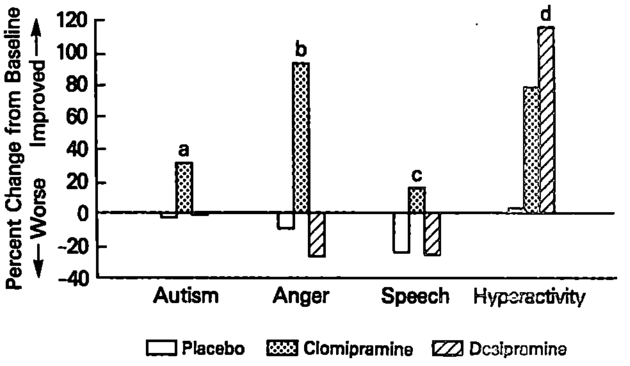
[a] Fourteen-item autism-relevant subscale.
[b] Scores at week 5 of treatment.
[c] Week 3 score; subject discontinued desipramine treatment after 3 weeks because of severe behavioral deterioration.
[d] $F=20.77$, $df=3, 18$, $p=0.0003$.
[e] $F=14.89$, $df=3, 18$, $p=0.002$.

uptake blocker, was differentially effective in treating autistic disorder compared with the primarily noradrenergic tricyclic desipramine. Obsessive-compulsive symptoms improved, as had been hypothesized given the differential response of these behaviors to serotonin reuptake blockers in obsessive-compulsive disorder. In addition—and unexpectedly—core autistic symptoms, as measured by the autism factor of the Children's Psychiatric Rating Scale, were improved differentially by clomipramine. The results of this study are consistent with a previous single case report of fluoxetine treatment of a 26-year-old autistic woman in which improvement in ritualistic behavior and other autistic symptoms was described (13). These findings have important clinical and theoretical implications.

Pharmacologic trials in autism to date have yielded relatively disappointing results. The most studied and consistently useful agent has been haloperidol (14), although it has been debated whether the type and magnitude of improvement shown in research is clinically significant (15), and side effects including tardive dyskinesia are problematic (16). Even though the sample size was small in our study, the consistency of the positive clinical effects of clomipramine was striking. Furthermore, the parents of all seven subjects chose to have their children continue taking clomipramine after completion of the study, indicating that the statistically significant improvements on the rating scales were clinically significant.

Worsening of behavior was reported in one-half of a group of 10 autistic and schizophrenic children during an open trial of imipramine, and this was cited as evidence for the detrimental effect of serotonin reuptake inhibition (17). The deterioration in behavior may have been due to reuptake inhibition of norepinephrine or other pharmacologic effects of imipramine. The clomipramine-induced improvement in our study was relative to both placebo and desipramine and not an artifact of behavioral deterioration during treatment with desipramine, the major metabolite of imipramine.

**FIGURE 1. Percent Change From Baseline in Scores of Seven Autistic Subjects on the Autism-Relevant Subscale Factors of the Children's Psychiatric Rating Scale in a Comparison of Clomipramine and Desipramine Treatment**



[a] $F=10.26$, $df=3, 15$, $p=0.02$.
[b] $F=5.03$, $df=3, 12$, $p=0.05$.
[c] $F=2.78$, $df=3, 15$, $p=0.12$.
[d] $F=4.62$, $df=3, 15$, $p=0.05$.

It is intriguing to speculate on the relation between clomipramine's serotonergic effects and its efficacy in autism. Reduced central serotonergic responsivity has been reported in autistic disorder (18), and clomipramine might enhance central serotonergic transmission, thereby improving clinical features of autism. However the effects of clomipramine on central serotonergic function remain unclear (19), and the serotonin-releasing agent fenfluramine has been extensively studied in autism (20) with equivocal results. The relation between clomipramine-induced improvement and platelet serotonin in our sample is presently under investigation.

Similarities in phenomenology and differential response to serotonin reuptake blocking drugs in obsessive-compulsive disorder, trichotillomania, onychophagia, and autistic disorder suggest similarities in underlying pathophysiology. Central serotonergic dysfunction might be related to impulsive, ritualistic behavior in general, independent of diagnostic categories.

Behavioral symptom patterns in autism are often cyclic, potentially complicating the findings derived from relatively brief medication trials. It is common for transient clinical improvements to occur shortly after the introduction of a new medication. However, this seems unlikely to have occurred in this study, since desipramine treatment did not result in similar benefit.

These preliminary results need to be extended with a larger sample and a longer-term clomipramine treatment period, as well as with short-term, double-blind placebo comparisons. Such studies are presently underway.

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# Serum Prolactin Levels in Homosexual and Bisexual Men With HIV Infection

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*Objective: Prolactin is a neurohormone that may be secreted in response to stress and also has regulatory effects on the immune system. Some, but not all, studies suggest that prolactin levels are higher than normal in persons with HIV infection. The authors measured prolactin levels in HIV-positive and HIV-negative homosexual and bisexual men to assess possible differences in levels and then examined relationships between prolactin level and measures of medical status, anxiety, depression, stress, and neuropsychological test performance. Method: Blood for prolactin level determination was obtained from 121 HIV-seropositive and 79 HIV-seronegative homosexual and bisexual men enrolled in a longitudinal study. The men also underwent a daylong assessment that included medical, immunological, psychiatric, psychosocial, psychosexual, and neuropsychological evaluations. Results: There was no statistically significant difference in serum prolactin level among the seronegative men, the seropositive men with no or minimal physical symptoms, and the seropositive men with significant physical symptoms of HIV infection. Furthermore, within the HIV-seropositive group, the correlations between serum prolactin level and measures of depression, anxiety, stress, and neuropsychological test performance were all nonsignificant. Conclusions: Serum prolactin level does not seem to respond to HIV infection or to be related to stress or psychiatric symptoms in HIV-infected men. As none of the subjects had AIDS, the possibility cannot be ruled out that prolactin level increases in very late stages of HIV infection.*

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The human immunodeficiency virus (HIV) produces disruption in almost every aspect of immune function, ultimately leading to an inability to contain opportunistic infection and neoplastic cell growth. It is clear, however, that a variety of responses are mounted against HIV by the infected host and, at least in early stages, contain the virus's ability to create immunological collapse. Neuroendocrine factors are known to have a role in regulating immune function, and recent work has examined possible ways in which the hypothalamus and pituitary gland may respond to HIV infection.

Prolactin is one hormone of particular interest because it is believed to have significant interaction with immune function (1–4) and may also be released during stress (5–8). High prolactin levels have also been implicated in panic disorder (9), psychosis (10), and alcoholism with psychosis (11). In all cases, the differences in prolactin level are modest.

A few studies have examined prolactin levels in patients with HIV infection. Croxson et al. (12) measured the prolactin levels of 85 homosexual men. The mean prolactin levels of patients with AIDS and patients with AIDS-related complex were significantly higher than that of seronegative men. The difference in prolactin level between asymptomatic HIV-positive and HIV-negative men was not significant. Nelson et al. (13) also found a higher mean prolactin level in a group of 48 HIV-infected men than in either a group of 13 HIV-negative homosexual men or a group of 14 men described by them as "normal heterosexuals." Three small studies (14–16) showed no relationship between prolactin level and HIV infection.

The literature therefore suggests that prolactin level may increase with increasing severity of HIV infection, and there are theoretical reasons to believe that prolac-

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tin level may increase with stress or psychiatric illness and play a role in immune function. As part of a longitudinal, multidisciplinary study of patients with HIV infection, we obtained blood for prolactin level determination from HIV-seropositive and HIV-seronegative homosexual and bisexual men during a baseline evaluation that included medical, immunological, psychiatric, psychosexual, and neuropsychological assessments. In our relatively large study group we looked for differences in prolactin level among groups stratified for degree of illness severity. Furthermore, we analyzed the data to determine relationships between prolactin level and measures of illness severity, stress, and psychiatric symptoms.

## METHOD

### *Subjects*

The subjects of this report are all enrolled in an ongoing study of HIV infection and are described in more detail elsewhere (17). When the study was initiated in 1988, the cohort of homosexual and bisexual men included 123 HIV-seropositive and 84 HIV-seronegative subjects. One HIV-seropositive subject previously included in the cohort actually had AIDS at the baseline assessment according to information subsequently received and has therefore not been included here. The subjects are seen every 6 months for a daylong evaluation that includes medical history and physical examination, neurological examination, neuropsychological testing, and psychiatric and psychosexual interviews. Blood is obtained for lymphocyte subset analysis, serum p24 antigen level determination, and confirmatory HIV testing. Serum from every subject is then frozen. Urine is also obtained for 24 hours to determine urinary free cortisol level. All subjects signed informed consent statements before testing.

To be included in the study, a subject was required to have known his HIV status for at least 1 month and to have not used intravenous drugs more than 10 times since 1981. HIV-seropositive subjects at all stages of the illness were enrolled, but subjects who already had histories or evidence of opportunistic infection or secondary tumors that met the CDC National Surveillance Criteria for AIDS (18) were excluded.

Of the 123 HIV-seropositive and 84 HIV-seronegative men assessed at baseline, serum samples sufficient for prolactin level determination were available for 121 and 79, respectively. The mean ages of the two groups were not significantly different: 38.4 years (SD=8.2) versus 37.5 years (SD=8.7) ($t=-0.71$, $df=198$, $p=0.48$).

### *Procedure*

The medical history was obtained from each subject by a research nurse who was not blind to HIV status and used a structured interview focusing on HIV-related symptoms. Although the physician who performed the physical examination followed a semistructured format that also focused on HIV-related signs, the physician was blind to the subject's HIV status. The stage of HIV infection was rated according to standard CDC criteria (19).

The numbers of $CD4^+$ and $CD8^+$ T lymphocytes in peripheral blood were determined with a fluorescent activated cell sorter on mononuclear cell populations.

Psychiatric examination was performed by a trained mental health professional who was not blind to HIV status. This assessment included the Structured Clinical Interview for DSM-III-R (SCID) (20) and a battery of rating scales. Here we report results on the Hamilton Rating Scales for Depression and for Anxiety (21), a demoralization scale from the Psychiatric Epidemiology Research Interview (PERI) of Dohrenwend (22), the Beck Hopelessness Scale (23), and a modified version of the Faschingbauer et al. Texas Revised Inventory of Grief (24). Further details on our use of these scales can be found elsewhere (25, 26).

Neuropsychological testing was performed by a trained technician blind to HIV status and included a battery of tests described in detail elsewhere (27). Performance on each test was compared to the norm for an age- and education-matched population and then rated as normal, borderline (at least one standard deviation below expected mean), or defective (at least two standard deviations below the expected mean). A clinical impression of neuropsychological performance (normal, borderline, or abnormal) was based on the consensus of two experienced neuropsychologists who reviewed the test scores independently and were blind to HIV status.

Serum prolactin levels were determined from stored frozen serum. The protocol called for blood to be obtained from each subject between 8:30 and 11:00 a.m. Occasionally, for technical and scheduling reasons, a blood sample was obtained from a subject later in the day, but no record of this was kept. The nurses responsible for phlebotomy reported that in more than 90% of the cases blood samples from this cohort were obtained in the morning and that any breaches in the protocol occurred at random with respect to the subjects' HIV status.

Serum prolactin was measured with double antibody radioimmunoassay (28). The prolactin standard (hPR1-RP-1) and the primary antiserum were donated by the National Pituitary Agency (National Institute of Arthritis, Metabolism and Digestive Diseases). The $^{125}$I-labeled PR1 was repurified before use on a G-100 Sephadex column. Anti-rabbit-globulin serum was used to separate the bound and free fractions. The samples were assayed in duplicate. The intra- and interassay coefficients of variance were 6.37% and 6.86% at 3.8 ng/ml, 3.83% and 5.72% at 27.0 ng/ml, and 2.01% and 3.49% at 46.3 ng/ml.

To test for differences in serum prolactin level, we divided the subjects into three groups: HIV seronegative, HIV seropositive with no symptoms or only enlarged lymph nodes (CDC stages II and III), and HIV seropositive with more serious symptoms (CDC stages

**TABLE 1. T Cell Concentrations and Test Scores of HIV-Positive and HIV-Negative Homosexual and Bisexual Men**

| | HIV-Positive Men | | | HIV-Negative Men | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | T Cell Concentration (cells/μl) or Test Score | | | T Cell Concentration (cells/μl) or Test Score | | | Significance | | |
| Variable | Mean | SD | N | Mean | SD | N | t | df | p |
| T cell measure | | | | | | | | | |
| $CD4^+$ | 409.0 | 222.6 | 120 | 843.1 | 263.7 | 79 | 12.50 | 197 | 0.000 |
| $CD8^+$ | 829.0 | 435.3 | 120 | 549.9 | 202.6 | 79 | –5.33 | 197 | 0.000 |
| CD4/CD8 ratio | 0.58 | 0.36 | 120 | 1.67 | 0.62 | 79 | 15.67 | 197 | 0.000 |
| Tests | | | | | | | | | |
| Hamilton depression scale | 4.25 | 4.16 | 120 | 3.16 | 3.51 | 79 | –1.91 | 197 | 0.06 |
| Hamilton anxiety scale | 3.85 | 3.84 | 104 | 2.81 | 3.60 | 78 | –1.86 | 180 | 0.07 |
| PERI demoralization scale | 28.22 | 14.90 | 117 | 24.00 | 13.09 | 78 | –2.03 | 193 | 0.04 |
| Beck Hopelessness Scale | 5.42 | 4.94 | 116 | 3.21 | 3.16 | 78 | –3.50 | 192 | 0.001 |
| Texas grief inventory | 29.33 | 10.98 | 108 | 28.90 | 10.18 | 77 | –0.27 | 183 | 0.79 |
| Neuropsychologists' impression | 0.50 | 0.67 | 121 | 0.43 | 0.67 | 79 | –0.67 | 198 | 0.50 |

IVa, IVb, IVc-2, and IVe). A three-group analysis of variance (ANOVA) was performed.

To test for a relationship between serum prolactin level and severity of HIV infection, we computed Pearson correlation coefficients within the HIV-positive group for the correlations between prolactin level and both number of $CD4^+$ T lymphocytes and ratio of $CD4^+$ to $CD8^+$ T lymphocytes (CD4/CD8).

To test for a relationship between psychological state and prolactin level, we computed Pearson correlation coefficients for the relationship between prolactin level and scores on the Hamilton depression scale, Hamilton anxiety scale, PERI demoralization scale, Beck Hopelessness Scale, and Texas Revised Inventory of Grief within the HIV-positive group. Finally, we determined the correlation between prolactin level and score on the neuropsychologists' impression within the HIV-seropositive group.

All p values are two-tailed. The number of subjects varies among measures because of missing data.

## RESULTS

Table 1 indicates that the HIV-positive patients had significantly fewer $CD4^+$ T cells, significantly more $CD8^+$ T cells, and a significantly lower CD4/CD8 ratio. The HIV-positive subjects had significantly higher demoralization and hopelessness scores and nearly significantly higher anxiety and depression scores than the HIV-negative subjects. The clinical neuropsychological impression and grief scores were not significantly different.

Only six (5%) of the HIV-positive subjects were taking zidovudine at the time of the baseline assessment, and we did not observe any relationship between zidovudine use and prolactin level in this small subgroup. Of other medications taken by the subjects in the study, only the antipsychotic drugs have, to our knowledge, a known effect on prolactin level. However, only two of the 121 HIV-positive men and one of the 79 HIV-negative men were taking these drugs.

Forty-seven (39%) of the seropositive men were in CDC stage II (asymptomatic), 28 (23%) were in CDC stage III (enlarged lymph nodes), and 46 (38%) were in CDC stage IVa, IVb, IVc-2, or IVe. The subjects were divided into three groups: 1) HIV-seronegative, 2) HIV-seropositive—asymptomatic/lymphadenopathy, and 3) HIV-seropositive—symptomatic. Three-group ANOVA of serum prolactin level revealed no significant difference among these groups; the mean levels were 9.2 (SD=3.2), 10.2 (SD=3.4), and 9.9 (SD=3.9) ng/ml, respectively (F=1.47, df=2, 197, p=0.23).

**TABLE 2. Correlation of Prolactin Level With T Cell Concentrations and Test Scores for 12 HIV-Positive Homosexual and Bisexual Men**

| | Correlation With Prolactin Level | | |
|---|---|---|---|
| Variable | r | df | p |
| T cell concentrations | | | |
| $CD4^+$ | –0.07 | 118 | 0.42 |
| CD4/CD8 ratio | –0.15 | 118 | 0.11 |
| Test scores | | | |
| Hamilton depression scale | –0.07 | 118 | 0.44 |
| Hamilton anxiety scale | –0.08 | 102 | 0.41 |
| PERI demoralization scale | –0.06 | 115 | 0.54 |
| Beck Hopelessness Scale | –0.07 | 114 | 0.47 |
| Texas grief inventory | –0.01 | 106 | 0.88 |
| Neuropsychologists' impression | 0.10 | 119 | 0.26 |

Table 2 indicates that within the HIV-positive group the correlations between serum prolactin level and number of $CD4^+$ T cells, CD4/CD8 ratio, anxiety, depression, demoralization, hopelessness, grief, and neuropsychological performance were all nonsignificant.

## DISCUSSION

We did not find higher than normal prolactin levels or a significant correlation between severity of infection and prolactin level in our HIV-seropositive men. Furthermore, we did not observe any relationship between prolactin level and measures of anxiety, depression, or neuropsychological test performance.

Like other groups of subjects (26), our group of HIV-positive subjects was relatively free of psychiatric illness at baseline, and none had AIDS. Without severely anxious, depressed, or medically ill individuals, we may have been limited in our ability to detect a relationship between psychological or medical state and prolactin level.

In an earlier report involving the same subjects (29), we found no significant difference between HIV-positive and HIV-negative homosexual and bisexual men in the level of 24-hour urinary free cortisol. The present findings on prolactin level are similar and, despite the cautions mentioned, suggest that prolactin level, like urinary cortisol level, is not altered in the earlier stages of HIV infection. Nevertheless, it is still conceivable that HIV, because it infects both the immune and the nervous systems, may disrupt normal relationships between neurohormones and immune function, as noted elsewhere (30). Future studies of prolactin's role in the immune response of HIV-infected patients should focus on more advanced stages of illness, functional measures of immune response (such as mitogen stimulation studies), and patient groups other than homosexual men.

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# Prevalence of Cocaine Use Among Residents of New York City Who Committed Suicide During a One-Year Period

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*Objective: In the mid-1980s the form of cocaine called "crack" became widely available in New York City. The authors sought to determine the prevalence of cocaine metabolites detected at autopsy in persons who committed suicide in New York City during this period. Method: Individual reviews of the autopsy and toxicological records of all persons under the age of 61 who had committed suicide in the city during a 1-year period were conducted to determine demographic characteristics, suicide methods, and cocaine and alcohol use at the time of death. Results: In one of every five cases studied, the person who committed suicide had used cocaine within days of his or her death. The prevalence of cocaine use among young Hispanic males who committed suicide was 45%. Persons who were young, black, or Hispanic and who had used alcohol immediately before the fatal injury were most likely to have been recent cocaine users. After controlling for demographic variables and ethanol use, the investigators found that individuals who committed suicide with firearms were twice as likely to have used cocaine as those who used other methods. Conclusions: In contrast to the results of regional and household surveys during this period, which suggested that the current prevalence of cocaine use in New York City was 3%–5%, these results suggest a high prevalence of cocaine use in the days immediately preceding death by young persons who commit suicide. Additional studies are needed to determine how cocaine may act as a risk factor for suicide.*

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Much recent attention has been properly focused on the association between cocaine use and rising homicide rates. However, the link between cocaine use and suicide has not been adequately investigated. Several studies have shown that chronic cocaine users experience intense suicidal ideation, particularly in the withdrawal phase, which can last for several days immediately following a cocaine binge (1–3). In addition, alcohol abuse, a major risk factor for suicide, is common among cocaine users (2).

Evaluation of the role of cocaine in suicide assumes added urgency in view of both the large proportion of polysubstance abusers among young persons who commit suicide and the rising suicide rate in the 1960s and 1970s among young males (4). The San Diego Suicide Study, conducted in the early 1980s, found that 30% of the persons under age 30 who committed suicide had histories of cocaine use, but it did not estimate the prevalence of cocaine use either at autopsy or in the general community (4). In 1986, 7% of all cocaine-positive deaths in New York City were suicides (5).

By 1985 a new, potent, inexpensive, smokable alkaloidal form of cocaine called "crack" had become widely available in New York City. The purpose of this study was to determine the prevalence of cocaine use among persons who committed suicide and the demographic characteristics of this group during this crack epidemic.

## METHOD

All cases certified as suicides by the New York City medical examiner that occurred among city residents during the calendar year 1985 were eligible for the study. This year was chosen because it corresponded to the latest full calendar year immediately before the most recent regional survey of cocaine use among the general

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population of New York City. A list of all suicides classified according to *ICD-9* codes E950 through E959 was provided by the Office of Biostatistics of the New York City Health Department. Cases of individuals who were not residents of New York City but committed suicide within its geographic boundaries and cases of residents whose suicides were certified in other jurisdictions were not eligible for the study. In addition, cases in which the manner of death was certified as "undetermined" (*ICD-9* codes E980–E989) were ineligible. The medical examiner's records were individually reviewed in their entirety at the Office of the Chief Medical Examiner of New York City to ascertain demographic data; time, date, and location of injury, death, and autopsy; results of police and medical examiner investigations; previous hospital records if available; and toxicological findings.

For the purpose of determining the demographic characteristics related to cocaine use and suicide, we confined our analysis to persons aged 60 years or less who had been screened for cocaine at autopsy and who had died within 48 hours after a self-inflicted injury. Previous studies have shown that the prevalence of cocaine metabolites detected at autopsy in persons older than 60 is negligible (5, 6).

Survival time, defined as the period from self-inflicted injury to death, was also determined for all individuals who had received medical care prior to their deaths. A survival time in excess of 48 hours prohibits inferences about cocaine use at the time of lethal injury. A number of studies have shown that little cocaine metabolite is detectable in urine, by homogeneous enzyme assay at detection limits of 0.3 mg/liter, beyond 48 hours (7–9). Other studies suggest that metabolites can be detected in heavy users up to 120 hours or more after use (10, 11). In practice, this discrepancy in detection time had little appreciable effect on this sample of suicides, as the vast majority of individuals died within 48 hours after injury. The small group that had prolonged survival times survived for longer than 120 hours. In some cases, the lethal injury was accomplished in secret, and the dead person was discovered hours to days following the injury. For these individuals who did not receive medical care after the injury, survival time was indeterminate but was presumed to be less than 48 hours.

Urine and blood specimens obtained at autopsy were stored at 4 °C until assay. The principal metabolite of cocaine, benzoylecgonine, was screened in urine samples by means of a homogeneous enzyme immunoassay. A sample was considered positive if benzoylecgonine was detected at a concentration of 0.3 mg/liter or more. Analysis was repeated on all positive urine specimens. In addition, substantiation of positive results in urine specimens was obtained by radioimmunoassay for cocaine and/or metabolites in blood.

In some cases in which urine was not readily available at autopsy, blood was screened by radioimmunoassay. Results were considered positive by radioimmunoassay if cocaine and/or benzoylecgonine were detected at concentrations greater than 0.1 mg/liter. Blood specimens considered positive by radioimmunoassay were, in addition, analyzed for cocaine by gas chromatography.

Head space gas chromatography was used to perform ethanol analysis. Specimens were considered positive if the blood ethanol concentration was 2 mmol/liter or more. In cases in which blood alcohol concentrations were 7 mmol/liter or more, gas chromatography was done to assess brain concentrations.

Data were analyzed with the SPSS and BMDP Statistical Software. Differences in proportions were assessed with chi-square tests, and analyses of variance were used to compare group means. A logistic regression analysis was done to examine the association of hypothesized predictors (sociodemographic characteristics and methods of suicide) and cocaine use. The logistic regression model was used to estimate the risk of cocaine use associated with each level of a given predictor, controlling for all other predictors. Statistical significance was defined as a two-tailed probability of less than 0.05.

## RESULTS

There were 749 cases of suicide among New York City residents in the study year, of which 570 involved persons aged 60 years or less. In this sample of 570 cases, 482 persons had survival times under 48 hours and were screened for cocaine. In the remaining 88 cases, excluded from this study, most persons had survival times that exceeded 48 hours, and in a few, toxicology screens were not available because of family objections to autopsy. Both the mean age and the racial composition of the smaller, excluded group (N=88) differed significantly from those of the study group (N=482): the excluded group was older (mean ages=41.7 years [SD=12.8] and 35.4 years [SD=10.8], respectively; F=24.21, df=1, 568, $p<0.0001$) and had more white and Asian persons ($\chi^2=19.9$, df=3, p=0.0002). There were no sex differences between these groups.

Cocaine metabolites were detected in 105 (21.8%) of the 482 persons who were 60 years of age or younger (95% confidence interval=18.1%–25.5%). By assuming that the excluded cases had negative toxicological findings for cocaine and/or benzoylecgonine, the minimum and most conservative prevalence estimate of recent cocaine use for the total sample under age 61 (N=570) was 18.4%, and for the total sample of all ages (N=749), it was 14.0%.

The demographic characteristics of the 482 persons who survived 48 hours or less after injury, grouped according to cocaine toxicology results, are shown in table 1. Ethanol was detected conjointly with cocaine in approximately half of the cases consistently across all demographic categories.

A logistic regression analysis was performed to test the effects of age, sex, race/ethnicity, suicide method, and alcohol use on the likelihood of recent cocaine use. Of these, age, race, use of firearms, and positive ethanol toxicology results were significant, but sex was not (table 2). When age, sex, alcohol use, and suicide method

**TABLE 1. Prevalence of Cocaine Metabolites and Alcohol Detected at Autopsy Among Persons Under Age 61 Who Committed Suicide[a]**

| Variable | N | Cocaine | | Cocaine and Alcohol | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| Total sample | 482 | 105 | 21.8 | 56 | 11.6 |
| Age (years) | | | | | |
| 11–20 | 33 | 7 | 21.2 | 2 | 6.1 |
| 21–30 | 153 | 44 | 28.8 | 23 | 15.0 |
| 31–40 | 141 | 35 | 24.8 | 19 | 13.5 |
| 41–50 | 107 | 15 | 14.0 | 10 | 9.3 |
| 51–60 | 48 | 4 | 8.3 | 2 | 4.2 |
| Sex | | | | | |
| Male | 358 | 87 | 24.3 | 44 | 12.3 |
| Female | 124 | 18 | 14.5 | 12 | 9.7 |
| Race/ethnicity | | | | | |
| White/Asian | 234 | 29 | 12.4 | 12 | 5.1 |
| Black | 118 | 28 | 23.7 | 5 | 12.7 |
| Hispanic | 130 | 48 | 36.9 | 29 | 22.3 |
| Suicide method (*ICD-9* code) | | | | | |
| Poisoning (E950) | 70 | 10 | 14.3 | 6 | 8.6 |
| Gases (E952) | 7 | 3 | 42.9 | 2 | 28.6 |
| Hanging (E953) | 93 | 26 | 28.0 | 9 | 9.7 |
| Drowning (E954) | 19 | 5 | 26.3 | 5 | 26.3 |
| Firearms (E955) | 115 | 41 | 35.7 | 23 | 20.0 |
| Lacerations (E956) | 14 | 1 | 7.1 | 1 | 7.1 |
| Jumping (E957) | 126 | 16 | 12.7 | 9 | 7.1 |
| Subway (E958) | 38 | 3 | 7.9 | 1 | 2.6 |

[a] Survival time was 48 hours or less after injury in all cases.

**TABLE 2. Logistic Regression Analysis for Variables Related to Cocaine Use and Suicide Among 482 Persons Under Age 61[a]**

| Variable | Odds Ratio | 95% Confidence Interval |
|---|---|---|
| Sex | | |
| Female | 1.00 | |
| Male | 1.45 | 0.80–2.62 |
| Race/ethnicity | | |
| White | 1.00 | |
| Black | 1.89 | 1.04–3.43 |
| Hispanic | 3.28 | 1.89–5.70 |
| Asian | 0.56 | 0.07–4.53 |
| Suicide method | | |
| All except firearms | 1.00 | |
| Firearms | 2.01 | 1.21–3.34 |
| Ethanol toxicology results | | |
| Negative | 1.00 | |
| Positive | 1.79 | 1.12–2.86 |

[a] Exponentiated regression coefficient for age=0.97 (95% confidence interval=0.95–0.99).

were controlled, Hispanic and black persons were 3.3 and 1.9 times as likely, respectively, as white persons to have used cocaine immediately before committing suicide (table 2). It is particularly noteworthy that when age, race/ethnicity, sex, and alcohol use were controlled, persons who used firearms to commit suicide were twice as likely to have used cocaine as individuals who used other methods. As shown in table 3, the prevalence of cocaine use rose with age across sex and racial/ethnic groups, peaking at ages 18–30, then fell dramatically after age 50. The highest prevalence of use (45.7%) was detected in Hispanic males aged 18–30 (table 3).

## DISCUSSION

The principal finding of this study is that in the mid-1980s, approximately one in five persons aged 60 years or less who resided in New York City and who committed suicide had used cocaine in the days prior to death. It has been hypothesized that the 150% increase in the suicide rate among young adults from 1960 to 1980 is explained in part by the high prevalence of drug use among young persons (4). Previous studies have found a relative risk of suicide among substance abusers ranging from five to 20 times that of the general population (12–14). Other studies suggest that the lifetime prevalence of suicide attempts among drug abusers ranges from 17% to 30% of cases, but whether suicide attempters and those who succeed in committing suicide constitute distinct or overlapping populations remains controversial (14–16). Most studies investigated the role of alcohol, sedative hypnotics, or opiates. However, this is the first study, to our knowledge, that has specifically investigated the use of cocaine immediately prior to suicide.

Our finding that the prevalence of cocaine use was greatest among individuals in their 20s and 30s is consistent with the results of other studies (17). Compared with "pure" alcoholics, cocaine users, like other substance abusers, commit suicide both at an earlier age and in a shorter time after initial drug use (4).

There were no significant sex differences in the prevalence of cocaine detected at autopsy. While this finding contrasts with those of other studies which show a higher proportion of drug use among males who commit suicide, we also found no sex difference in cocaine use among motor vehicle fatalities in New York City (6).

The high prevalence of cocaine use among black and Hispanic persons who committed suicide is interesting. Black males have traditionally had much lower suicide rates than white males, although in recent years this difference has been narrowing, particularly in younger age groups (18). Some observers have implicated drug use in these trends. It is uncertain why Hispanic individuals appear to be particularly vulnerable. One study found that almost two-thirds of suicide attempters of Puerto Rican descent had diagnoses of substance or alcohol abuse (19). That study and others of this population suggest that many young Hispanic persons attempt or commit suicide following arguments with their spouses or parents (20, 21). Whether a drug such as cocaine, with its potential for inducing irritability and paranoia, is more likely to set the stage for suicide in some cultural groups has not been determined.

The high conjoint prevalence of cocaine and alcohol use among persons who committed suicide (alcohol was detected in one-half of all the cocaine users at autopsy) is not surprising. In the San Diego study (4), 84% of substance users also used alcohol regularly. In addition, most studies suggest that drug-abusing individuals likely to commit suicide are polysubstance

**TABLE 3. Prevalence of Cocaine Metabolites Detected at Autopsy Among 482 Persons Under Age 61 Who Committed Suicide, According to Age, Sex, and Racial/Ethnic Group**

| | White/Asian | | | | | | Black | | | | | | Hispanic | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males (N=166) | | | Females (N=68) | | | Males (N=88) | | | Females (N=30) | | | Males (N=104) | | | Females (N=26) | | |
| | | Cocaine Detected | | | Cocaine Detected | | | Cocaine Detected | | | Cocaine Detected | | | Cocaine Detected | | | Cocaine Detected | |
| Age (years) | N | N | % | N | N | % | N | N | % | N | N | % | N | N | % | N | N | % |
| <18 | 4 | 0 | 0.0 | 1 | 0 | 0.0 | 2 | 0 | 0.0 | 0 | 0 | 0.0 | 1 | 0 | 0.0 | 1 | 0 | 0.0 |
| 18–30 | 53 | 12 | 22.6 | 21 | 5 | 23.8 | 45 | 13 | 28.9 | 15 | 3 | 20.0 | 35 | 16 | 45.7 | 8 | 2 | 25.0 |
| 31–40 | 49 | 6 | 12.2 | 16 | 0 | 0.0 | 18 | 5 | 27.8 | 5 | 1 | 20.0 | 44 | 19 | 43.2 | 9 | 4 | 44.4 |
| 41–50 | 37 | 4 | 10.8 | 20 | 0 | 0.0 | 15 | 4 | 26.7 | 8 | 1 | 12.5 | 21 | 5 | 23.8 | 6 | 1 | 16.7 |
| 51–60 | 23 | 1 | 4.3 | 10 | 1 | 10.0 | 8 | 1 | 12.5 | 2 | 0 | 0.0 | 3 | 1 | 33.3 | 2 | 0 | 0.0 |

abusers (17). The role of other drugs used conjointly with cocaine in enhancing suicide risk remains to be elucidated.

The association of cocaine-related suicides with firearms is striking. Firearms accounted for 39% of all suicides by cocaine-positive individuals but only 20% of all suicides in New York City. Similarly, 35.7% of all firearm suicides in New York were by cocaine-positive persons. It is possible that cocaine users are more likely than others both to own guns and to commit suicide.

How does the prevalence of cocaine use among persons who commit suicide compare with the prevalence of its use in New York City? A household telephone survey of drug abuse conducted for the Division of Substance Abuse Services included 6,368 respondents aged 18 years or older who were residents of the state (22). The sample, stratified by state region, included an oversample of Hispanic and young residents (groups at particular risk for substance abuse) as well as subsets of undergraduate college students, transients in shelters, and persons without telephones. Prevalences for current (the past 30 days), recent (the past 6 months), and lifetime cocaine use were 3%, 5%, and 13%, respectively. However, the survey relied on self-reported drug use, unlike this study of actual post-mortem toxicology results. Nevertheless, comparing the findings of that survey with our data suggests that cocaine use is considerably more common among individuals who commit suicide than in the general population of New York City.

The mechanism by which use of cocaine enhances suicide risk is unknown. However, any hypothesis must account for the marked comorbidity between drug use and psychiatric disorders such as depression, schizophrenia, and anxiety disorders, which are independently associated with suicide (23). Since the increased availability of cocaine in New York City in the mid-1980s has not been paralleled by marked contemporaneous increases in the overall suicide rate, it is likely that many persons using cocaine are already predisposed to suicide on the basis of other factors. Some authors suggest that predisposition to drug abuse and certain personality disorder symptoms (e.g., affective lability or impulsivity) may share a common biological or psychological substrate (24). Others argue that cocaine users are "self-medicating" underlying mental syndromes (25).

Any attempt to explain mechanisms will also need to elucidate both the timing of drug use in relation to the suicidal act and the presence of a dose-response effect. It is uncertain, for example, whether cocaine users are at highest risk in the intoxicated phase or in the withdrawal phase. Similarly, it is uncertain whether a heavy pattern of cocaine use is associated with an increased propensity to commit suicide.

Clinical reports suggest that those who may be at greatest risk are chronic, heavier users who experience withdrawal syndromes (2). These individuals report feeling edgy and dysphoric and may experience intense suicidal ideation. Prolonged use of cocaine results in marked depletion of neurotransmitters, including serotonin (26). A number of studies have found decreased concentrations of 5-hydroxyindoleacetic acid, the principal serotonin metabolite, in the CSF of suicide attempters who use violent means of self-destruction (27). Other psychostimulants, particularly amphetamines, that have pharmacologic actions similar to that of cocaine have also been linked to suicide (28). This suggests the intriguing but unproven hypothesis that psychostimulants may enhance suicide risk directly by changing brain neurochemistry. Substance abusers are also subject to intense psychosocial stressors, including deteriorating physical health, marital discord, legal and financial difficulties, and unemployment, all of which have been identified as potentiators of suicide (23).

There are several methodological issues that warrant comment. First, this study provided information about prevalence of cocaine use at one point in time at one location. American cities may differ significantly in the prevalence of illicit drug use over time (29). Our results may be substantiated in other urban centers where crack cocaine is widely available, but they may not apply to more rural areas.

In this study a person who committed suicide was considered cocaine positive on the basis of metabolite screening at autopsy. Metabolite assays establish use only within several days of death and provide no information about dosage, frequency of use, lifetime pattern of use, or recency of use. Assays alone do not establish the diagnosis of cocaine abuse or dependency. Presumably, a number of the cocaine-negative suicide cases in fact involved current, recent, or lifetime users of the drug.

Although not all persons who committed suicide were screened for cocaine or had survival times that allow inferences about cocaine use at the time of lethal injury, it is unlikely that artifacts of cocaine surveillance significantly affected our estimate of prevalence, since the conservative assumption that all excluded cases were cocaine negative would still result in a prevalence as high as 18%.

Finally, ascertainment bias, which refers to the criteria used to establish a diagnosis of suicide, is particularly important in studies of drug-abusing populations. We chose to examine only certified suicides. Many cocaine users die in "accidents" or with self-inflicted injuries of unknown intent, or the circumstances of death are indeterminable. These individuals and those who died of overdoses of illicit drugs (i.e., chronic or acute narcotism) were not included in this study.

We believe that there are several clinical implications of our study. First, cocaine users should be presumed to be at increased risk of suicide, and careful suicide histories should be taken. Since obtaining the drug is both illegal and dangerous, many users and dealers own firearms. The strong connection among firearms, suicide, and cocaine use underscores the need for clinicians to inquire about access to guns and make efforts for their removal.

It is likely that suicidal behavior represents only one type of self-destructive, violent behavior associated with cocaine use along a spectrum that includes accidents, criminal activities, and homicide. The probability of suicide among cocaine users needs to be assessed in terms of comorbid psychiatric diagnoses, patterns of use, dosage, and concurrent psychosocial stressors. Identification of those at greatest risk for suicidal ideation is essential before specific treatment interventions can be designed and implemented.

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# High Cholesterol Levels in Patients With Panic Disorder

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*Objective: This study was undertaken to help clarify whether the higher cholesterol levels found in patients with panic disorder are a complication of panic disorder only or are associated with any psychiatric disorder. Method: The subjects of the study were 30 patients with panic disorder and 30 patients with major depression, diagnosed according to the Structured Interview for DSM-III-R, and 30 normal control subjects. The three groups were matched for sex and age, and none of the subjects had alcohol/drug abuse, abnormal ECGs, or unstable medical conditions. Blood samples were drawn at random times, and serum cholesterol levels were determined. Results: The patients with panic disorder had significantly higher serum cholesterol levels than did the patients with major depression and the normal control subjects. Among the patients with major depression, histories (current or past) of anxiety disorders were associated with significant elevation of serum cholesterol levels. The presence of stable medical conditions was not associated with higher cholesterol levels in any of the three groups of subjects. Conclusions: Higher cholesterol levels were particularly associated with panic disorder in comparison with major depression. Higher levels of cholesterol in panic disorder are hypothesized to be a result of increased noradrenergic activity, which may be the underlying biological/neurochemical mechanism for symptoms of panic disorder, including anticipatory anxiety.*

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Hayward et al. (1) reported that a higher than expected number of female patients with panic disorder had cholesterol levels that exceeded the 75th percentile of national reference values. A high cholesterol level is a risk factor for coronary heart disease; therefore, that finding has significant medical implications and requires further study. Since panic disorder was the only psychiatric diagnosis that was investigated in the Hayward et al. study, it is unclear whether a higher cholesterol level is a complication of panic disorder or an artifact associated with any psychiatric diagnosis. To clarify this issue, we compared the serum cholesterol levels of patients with panic disorder to those of age- and sex-matched patients with major depression and normal control subjects.

## METHOD

The patients with major depression and the patients with panic disorder in this study came for outpatient treatment at a hospital psychiatry department. The normal control subjects were recruited through a newspaper advertisement soliciting volunteers for research studies. The two groups of patients received diagnoses according to the Structured Clinical Interview for DSM-III-R—Patient Edition (2). They had been drug free for a period of 3 weeks. The normal control subjects were screened for the presence of psychiatric disorders by mental health professionals. The patients and the control subjects were given ECGs and routine blood tests (CBC, SMA-18, VDRL, and thyroid function tests). Cholesterol levels were assessed as part of routine screening on admission. The blood samples for determining cholesterol levels were drawn at random between 10:00 a.m. and 5:00 p.m. The subjects were not given any instructions to change their usual dietary habits. Although it is desirable to obtain blood for cholesterol assessment after a 12-hour fast, it has been reported that mean plasma cholesterol concentration is unchanged after a fat-rich meal (3). Cholesterol levels were assessed with a TECHNICON SMAC 3 system

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**TABLE 1. Characteristics of Patients With Panic Disorder, Patients With Major Depression, and Normal Control Subjects[a] in a Study of Cholesterol Levels**

| | Patients With Panic Disorder (N=30) | | Patients With Major Depression (N=30) | | Normal Control Subjects (N=30) | | Analysis | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Mean | SD | Mean | SD | Mean | SD | F | df | p |
| Age (years) | 37.7 | 10.6 | 38.2 | 10.7 | 36.2 | 12.1 | 0.26 | 2, 87 | <0.77 |
| Weight (lb) | 159.5 | 37.1 | 156.4 | 39.6 | 153.2 | 24.1 | 0.24 | 2, 87 | <0.78 |
| Height (inches) | 66.1 | 4.2 | 65.8 | 4.3 | 67.8 | 4.1 | 1.88 | 2, 87 | <0.16 |
| Body mass index | 2.3 | 0.4 | 2.4 | 0.5 | 2.4 | 0.5 | 0.94 | 2, 87 | <0.40 |
| Duration of illness (months) | 17.1 | 19.6 | 19.3 | 32.1 | | | 0.09 | 1, 58 | <0.77 |
| Cholesterol level (mg/dl) | 224.7[b] | 43.5 | 189.8 | 32.8 | 183.6 | 37.7 | 10.10 | 2, 87 | <0.001 |

[a] In the group with panic disorder, 18 were white, nine Hispanic, one black, and two Asian/other; in the group with major depression, 12 were white, 11 Hispanic, three black, and four Asian/other; in the group of normal control subjects, 16 were white, four Hispanic, seven black, and three Asian/other; for race/ethnicity, $\chi^2$=14.9, df=8, p<0.06.

[b] Significantly different from the patients with major depression and the normal control subjects (each p<0.002, Tukey's honestly significant difference).

(sensitivity=0.00103 absorbance unit/unit of concentration mg/dl).

The exclusion criteria for potential patient subjects and normal control subjects were alcohol/drug abuse or dependence within the past 6 months, abnormal ECG, and unstable medical conditions such as hypertension, diabetes mellitus, and asthma. The three study groups contained 30 subjects each.

## RESULTS

Table 1 presents the characteristics of the three groups. They were age- and sex-matched (17 male and 13 female subjects in each group) and similar in height, weight, body mass index (i.e., weight in pounds divided by height in inches), and duration of illness. None of the patients with major depression and none of the normal control subjects was using oral contraceptives; one woman in the panic disorder group was using oral contraceptive pills. As can be seen in table 1, the pretreatment cholesterol levels in the three groups were significantly different. Follow-up multiple comparisons (Tukey's honestly significant difference) revealed that the panic disorder patients' mean cholesterol level was significantly greater than that of the patients with major depression and that of the normal control subjects. The cholesterol levels of the patients with major depression were not significantly different from those of the normal control subjects.

Patients with major depression who had histories (current or past) of anxiety disorders (N=9, five of whom were female; three with generalized anxiety disorder, two with simple phobia, and four with panic disorder) had higher cholesterol levels than did patients with major depression without histories of anxiety disorders (N=21, eight of them female) (214.1 mg/dl and 179.3 mg/dl, respectively; t=2.99, df=28, p<0.006). The sex ratio between groups was not significantly different ($\chi^2$=0.78, df=1, p<0.38). Since age was a significant covariate with cholesterol (F=31.3, df=1, 86, p<0.0001), and patients with major depression who had histories of anxiety disorders were older than those without such histories (mean=45.7 years, SD=13.9, and mean=34.9 years, SD=7.2, respectively), an analysis of covariance was conducted to adjust for the effect of age on cholesterol. When the effect of age was covaried out, patients with major depression and histories of anxiety disorders still had a significantly higher mean cholesterol level than patients without such histories (F=4.85, df=1, 27, p<0.04).

Thirteen of the patients with panic disorder had stable medical conditions (e.g., mitral valve prolapse, bronchial asthma, hypertension, or gout), and 10 of the patients with major depression had stable medical conditions (hypertension, diabetes mellitus, peptic ulcer, or migraine). The cholesterol levels of the patients with medical diagnoses did not differ from those of the patients without medical conditions (206.7 mg/dl and 207.2 mg/dl, respectively; F=0.006, df=1, 58, p<0.94). When patients with medical conditions were excluded from the analysis, the cholesterol levels of the patients with panic disorder remained significantly higher than those of the patients with major depression (224.5 mg/dl and 193.1 mg/dl, respectively; t=2.43, df=35, p<0.02), even after covarying out the effect of age (F=6.35, df=1, 34, p<0.02).

To ensure that a comorbid medical disorder was not responsible for the elevated cholesterol levels of the patients with panic disorder, analyses were conducted with only healthy patients (i.e., those without medical diagnoses) and their age- and sex-matched normal control subjects. The cholesterol levels of the healthy patients with panic disorder (N=17) were significantly higher than those of the control subjects (224.5 mg/dl and 179.8 mg/dl, respectively; t=3.00, df=32, p<0.01). The cholesterol levels of the healthy depressed patients (N=20) were significantly higher than those of their age- and sex-matched control subjects (193.1 mg/dl and 170.0 mg/dl, respectively; t=2.38, df=38, p<0.05). Since comorbid anxiety disorders were significantly related to cholesterol levels in the patients with depression, analyses were conducted excluding the depressed patients with histories of anxiety disorders. There was no significant difference between the healthy depressed patients (N=16) and their age- and sex-matched control subjects (183.1 mg/dl and 167.1 mg/dl, respectively; t=1.56, df=30, $p<0.13$). Healthy depressed patients with histories of anxiety disorders (N=4) had significantly higher cholesterol levels than depressed patients without such histories (N=16) (233.3 mg/dl and 183.1 mg/dl, respectively; t=3.49, df=18, $p<0.01$). To ensure that this effect was not due to age, an analysis of variance with age as a covariate was conducted. The difference remained statistically significant (F=10.29, df=1, 17, $p<0.01$).

## DISCUSSION

Our results support findings of an earlier study by Hayward et al. (1) which demonstrated that patients with panic disorder have higher cholesterol levels than age- and sex-matched normal control subjects. In addition, our study found that higher cholesterol levels were particularly associated with panic disorder in comparison to major depression. Interestingly, histories of anxiety disorders in patients with major depression were associated with higher cholesterol levels. There are two possible explanations that may account for these findings. First, anticipatory anxiety may be responsible for the elevations in cholesterol levels of patients with panic disorder. These patients experience substantial anticipatory anxiety related to the stressful experience of panic attacks. Previous research has demonstrated that natural and experimentally induced stress results in a significant increase in cholesterol (4–7). This hypothesis would suggest that the presence of anxiety per se may increase the risk of coronary heart disease. Second, there have been several studies demonstrating increased noradrenergic activity in panic disorder (8, 9). It may be that higher cholesterol levels in patients with panic disorder are a result of induction of lipoprotein lipase by norepinephrine (1).

It should be noted that in this study, the cholesterol levels of the patients with panic disorder as a group remained within the normal range (150–250 mg/dl). In addition, we did not measure high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol levels, which are considered to be more specifically correlated with risk of coronary heart disease. Whether a mildly elevated cholesterol level is a prodrome or is directly related to morbidity and mortality from cardiovascular diseases is unknown. There is some evidence of high cardiovascular mortality among patients with panic disorder at long-term follow-up (10, 11). Further research is necessary to investigate the potential negative impact of elevated cholesterol levels in patients with panic disorder by measuring both LDL and HDL cholesterol levels and to examine whether the cholesterol level decreases after the disorder goes into remission with adequate treatment.

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# Racial/Ethnic Identity and Amount and Type of Psychiatric Treatment

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Objective: *The purpose of this study was to examine the relationship of racial/ethnic identity to the amount and type of psychiatric treatment received by white, black, Latino, and Asian patients in the Los Angeles County mental health system.* Method: *The patients studied (N=19,400) consisted of all adult inpatients and outpatients seen in all county mental health facilities between January 1983 and August 1988. Multiple regression analysis was used to test the relationship between race/ethnicity and four measures of treatment received: number of treatment sessions, treatment modality, treatment setting, and therapist's discipline. The covariates included in the analyses were age, sex, socioeconomic status, primary language, diagnosis, and measures of treatment when these were logical predictors and were not acting as dependent variables.* Results: *Race/ethnicity did not have a consistent significant relationship to the treatment variables studied. However, diagnosis had a consistent and highly significant relationship to all four measures of treatment. A psychotic diagnosis was related to receiving more treatment sessions, greater use of medication, greater use of inpatient treatment, and less treatment by a professional therapist. Socioeconomic status and primary language also had consistent and significant relationships to three of the treatment variables.* Conclusions: *In considering modifications to the service delivery system, clinicians must evaluate whether the type of treatment provided to psychotic patients is the treatment of choice in terms of effectiveness and efficiency or whether it involves bias in service delivery. Similarly, the issue of bias in treatment of lower socioeconomic patients must be addressed.*

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The question of whether there is a relationship between racial/ethnic group identity and the amount and type of psychiatric treatment received is approached from several perspectives in the clinical and research literature. One issue raised frequently is discrimination in the assignment of treatment. In a follow-up study of an earlier finding, Mollica and Milic (1) reported that lower-class patients received low-intervention treatments from nonprofessional staff. More than half of lower-class patients who sought treatment were discharged without a treatment assignment. Conversely, Lindsey and Paul (2) contended that black patients are overrepresented among admissions to public institutions and that this is related to their lower socioeconomic status and to institutional racial bias in assigning treatment. Supporting their argument, an examination of black and white patients admitted to a psychiatric hospital by the police found that more black than white patients were admitted (3). Black patients were more likely than white patients to receive neuroleptics, compulsory orders, outpatient appointments, and a diagnosis of schizophrenia and drug-induced psychosis. The differences found in clinical management were partially accounted for by differences in diagnosis.

Armstrong et al. (4) reported opposite findings. They found black patients to be less impaired than white patients, to be underrepresented, to terminate treatment earlier, and to receive equal services. However, they found that more black than white patients were referred by the criminal justice system. Finally, Robinson and Johnson (5) noted that the effect of deinstitutionalization in the black community has been a significant increase in penal incarcerations.

Underutilization of mental health service—defined as a failure to seek treatment—has been noted for black, Latino, and Asian populations. Despite similar rates of psychosocial dysfunction, Mexican Americans have been reported to use mental health services proportionately less than Anglos (6–8). Sue and Sue (9) observed

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that Asians do not seek psychiatric treatment until their illness is severe. Several investigators (10–12) have reported that blacks in the United States do not use mental health services at the same rate as whites for similar psychiatric problems. Underutilization defined in terms of retention of patients in treatment according to therapists' recommendations for therapy has also been noted for black, Latino, and Asian patients, who have been observed to terminate treatment earlier than whites (4, 9, 13, 14).

The issue of the relationship of race/ethnicity to the amount and type of psychiatric treatment received is complex, involving not only the patient's race/ethnicity but also the patient's diagnosis, socioeconomic status, and other personal characteristics as well as several characteristics of treatment. In a further attempt to clarify the relationship of race/ethnicity to the type and amount of psychiatric treatment received, we examined white, black, Latino, and Asian patients in the Los Angeles County mental health system and four measures of psychiatric treatment: number of treatment sessions, treatment modality, treatment setting, and therapist's discipline. The relationships of age, sex, socioeconomic status, primary language, and diagnosis to the four measures of treatment were also examined.

## METHOD

Race/ethnicity was designated by each patient as non-Hispanic white, non-Hispanic black, Latino/Hispanic, and Asian/Pacific Islander. These groups were classified for analysis as white, black, Latino, and Asian.

The sample consisted of adult (18 years old and older) outpatients and inpatients seen in Los Angeles County mental health facilities between January 1983 and August 1988. Approximately equal numbers of white, black, Latino, and Asian patients were included in the total sample, which comprised all Asian patients seen during this time period and a random sample of equal numbers of Latino, white, and black patients. (Patients were included only if they had completed treatment; no patients were counted twice.) The total sample included 19,400 patients; 12,889 (66.6%) of these were outpatients and 6,511 (33.4%) were inpatients. For the entire Los Angeles County mental health system, 43.0% of the patients seen during the 5-year period were white, 20.5% were black, 25.5% were Latino, and 3.1% were Asian. According to 1985 census data, the population of Los Angeles County was 44.2% white, 12.8% black, 33.7% Latino, 8.7% Asian, and 0.6% all others.

The mean age of our entire sample was 33.5 years (SD=12.0). For whites, the mean age was 35 (SD=12.7), for blacks, 32.7 (SD=11.2), for Latinos, 32.3 (SD=11.9), and for Asians, 33.8 (SD=12.1). Tukey's honestly significant difference test was used to determine significant differences in age among the racial/ethnic groups. All pairwise comparisons were significant ($p \le 0.05$) except between blacks and Latinos. In the entire sample, 9,655 (49.8%) of the subjects were women and 9,745 (50.2%) were men. Among the white patients, 2,768 (51.7%) were women, among the black patients, 2,372 (44.5%), among the Latinos, 1,959 (49.8%), and among the Asians, 2,556 (53.5%). Comparisons of the racial/ethnic groups with one another on all other characteristics were made by using tests of proportions. For these analyses, the Bonferroni-adjusted alpha level of 0.008 was used to control for the simultaneous error rate that occurs when multiple comparisons are made. Black patients differed significantly from all of the other groups in sex; Latinos and Asians differed significantly from each other in sex.

Our measure of socioeconomic status of the subjects was based on the MediCal eligibility index. The MediCal index is determined by monthly family income and by number of dependents. We sorted the patients by whether they were eligible for MediCal (low income) or not: 15,157 (78.1%) of the patients were eligible for MediCal, and 4,243 (21.9%) were not. Among the whites, 3,991 (74.6%) were eligible, among blacks, 4,476 (84.0%), among Latinos, 3,169 (80.8%), and among Asians, 3,521 (73.8%). Tests of proportions revealed significant differences between all of the possible pairwise comparisons except between whites and Asians.

The primary language of each patient was categorized as English or other. For this variable, data were missing for 3,736 (19.3%) of the patients; the missing data were distributed proportionately among the racial/ethnic groups. There were 15,664 patients with complete information on this variable. The primary language was English for 4,426 (98.7%) of the whites, for 3,956 (97.5%) of the blacks, for 1,764 (56.7%) of the Latinos, and for 1,639 (40.9%) of the Asians. There were significant differences between all the possible pairings except between whites and blacks.

Diagnoses were made on standardized admission interview forms by therapists who were trained in the use of *DSM-III* diagnostic criteria. Diagnoses are routinely categorized three different ways in the Los Angeles County data system: 1) into multiple specific diagnostic categories, 2) into nine compressed categories, and 3) into dichotomized categories of psychotic and nonpsychotic. Psychotic diagnoses include schizophrenic disorders, paranoid disorders, psychotic affective disorders, and other psychotic disorders. For this analysis the dichotomized categories of psychotic and nonpsychotic were used. Of the entire sample, 11,216 (57.8%) were diagnosed as psychotic and 8,184 (42.2%) were diagnosed as nonpsychotic. Among whites, 2,942 (55.1%) were diagnosed as psychotic, among blacks, 3,348 (62.9%), among Latinos, 1,883 (47.9%), and among Asians, 3,043 (63.8%). Significant differences occurred in all the possible pairings except between blacks and Asians.

Data for the study originated from the Automated Information System currently in use by the Los Angeles County Department of Mental Health. The Automated Information System provides data for management information, revenue collection, clinical management, and monitoring with the potential for research. Data are collected routinely on each patient who contacts the county mental health system. Patient information is collected on standardized forms by the therapist and then transferred to a computerized file by a clerk. Patient files include information on demographics, clinical course, type and extent of services used, and agency or service provider.

The validity of the Automated Information System data is controlled through a variety of mechanisms. First, all data are entered into the Automated Information System through a fixed format screen. Second, values that are out of a given range as well as certain logical and substantive inconsistencies cannot be entered. Third, both the state and the county conduct program audits and program evaluations. Finally, the Los Angeles County Department of Mental Health monitors and reviews Automated Information System operations and data entry. Variables of interest to this study are routinely monitored through these means.

The reliability of the Automated Information System data has not been assessed systematically by the Los Angeles County Department of Mental Health. The reliability of some of the variables included in this study are of concern. For example, the reliability of diagnosis has been discussed in the literature (15, 16). Both the stability of diagnosis over time and the variability of diagnosis related to its use have been addressed. It is possible that reliability may be lower in clinical than in experimental settings. However, in this study, the treatment measures examined were dichotomized in the analysis; reliability would be expected to be higher in this situation.

## RESULTS

Least squares regression analysis was used to test the relationship of race/ethnicity to the amount and type of psychiatric treatment received for continuous variables, and logistic regression analysis was used for categorical variables. Four measures of psychiatric treatment served as dependent variables: number of sessions with the primary therapist, treatment modality, setting of treatment, and therapist's discipline. The covariates included in the analyses were age, sex, socioeconomic status, diagnosis, and treatment measures that might be considered logical predictors when they were not acting as the dependent variable in each regression model. For the regression analyses, the patients included were those with complete information on all the study variables (notably, primary language).

Least squares regression analysis was used to test the relationship of race/ethnicity and seven covariates to the number of sessions with the primary therapist. The distribution of this variable was positively skewed; therefore, log transformations were performed on the actual number of sessions with the primary therapist. However, the estimated relationship between predictors and the number of sessions was expressed in the original units by taking antilogs of the regression coefficients. The primary therapist was defined as the therapist who had the greatest number of sessions with the patient. For this variable, patients who were seen for assessment purposes only were excluded from the analysis (N=54). Additionally, since the primary therapist was not designated for the inpatients, the analysis included only outpatients.

The relationships of race/ethnicity, age, sex, socioeconomic status, primary language, diagnosis, therapist's discipline, and treatment modality to number of treatment sessions for the outpatients are displayed in table 1. The table shows that, compared with white patients, Asian patients had significantly more sessions, black patients had significantly fewer sessions, and Latino patients had close to the same number of sessions with the primary therapist.

Sex, socioeconomic status, primary language, diagnosis, therapist's discipline, and treatment modality were significantly related to number of sessions. Being female, having a professional therapist, and receiving medication were significantly related to a greater number of sessions with the primary therapist. Lower socioeconomic status, English as the primary language, and a psychotic diagnosis were significantly related to fewer sessions with the primary therapist.

Tukey's honestly significant difference test ($p \leq 0.05$) was used to provide a more detailed description of the relationship between the number of sessions with the primary therapist and each dependent variable. Test results for all the categorical variables supported the regression analysis. For this analysis, age was further categorized as younger (18–30 years), middle (31–50), older (51–64), and senior (65 and older). The middle and older age groups had significantly more sessions than either the younger or senior age groups.

Logistic regression analysis was used to test the relationship of race/ethnicity and the covariates to the other three dependent variables. The second dependent variable examined was treatment modality. This variable was categorized as therapy with medication or therapy without medication. Therapy with medication included medication plus talking therapy or medication therapy alone. Talking therapy alone was designated as therapy without medication. This analysis also included only the outpatients and excluded patients seen for assessment purposes only. Table 1 displays the relationship of race/ethnicity and six covariates to treatment modality. Black patients were significantly more likely to have medication prescribed than were white patients. Asian race/ethnicity and Latino race/ethnicity were not significantly related to treatment modality.

Socioeconomic status, primary language, diagnosis, and therapist's discipline were significantly related to treatment modality; age and sex were not. Lower socioeconomic status and English as the primary language were significantly related to not receiving medication therapy, and having a professional therapist was related to receiving medication therapy. Having a psychotic diagnosis was most strongly related to receiving medication therapy.

**TABLE 1. Relationship of Demographic and Clinical Variables to Treatment Characteristics for Patients in the Los Angeles County Mental Health System**

| | Relationship to Number of Sessions (N=10,599)[a] | | | Relationship to Treatment Modality (N=10,599)[a] | | | Relationship to Setting (N=15,610)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Effect[c] | p | 95% Confidence Interval | Effect[d] | p | 95% Confidence Interval | Effect[d] | p | 95% Confidence Interval |
| Race/ethnicity | | | | | | | | | |
| White (N=3,053)[e] | 1.00[f] | | | 1.00[f] | | | 1.00[f] | | |
| Asian (N=2,729)[g] | 1.15 | 0.0001 | 1.08–1.23 | 1.08 | 0.25 | 0.95–1.22 | 1.17 | 0.009 | 1.04–1.32 |
| Black (N=2,497)[h] | 0.81 | 0.0001 | 0.77–0.86 | 1.44 | 0.0000 | 1.28–1.61 | 0.93 | 0.12 | 0.84–1.02 |
| Latino (N=2,320)[i] | 0.95 | 0.14 | 0.90–1.01 | 1.11 | 0.10 | 0.98–1.26 | 1.31 | 0.0000 | 1.16–1.48 |
| Age | 1.00 | 0.39 | 1.00–1.00 | 1.00 | 0.12 | 1.00–1.01 | 1.03 | 0.0000 | 1.00–1.03 |
| Sex | 1.11 | 0.0001 | 1.07–1.15 | 0.95 | 0.22 | 0.88–1.03 | 1.16 | 0.0001 | 1.08–1.25 |
| Socioeconomic status | 0.80 | 0.0001 | 0.76–0.83 | 0.91 | 0.04 | 0.83–0.99 | 0.93 | 0.08 | 0.85–1.01 |
| Primary language | 0.85 | 0.0001 | 0.80–0.89 | 0.74 | 0.0000 | 0.66–0.83 | 0.90 | 0.07 | 0.81–1.01 |
| Diagnosis | 0.69 | 0.0001 | 0.67–0.72 | 3.10 | 0.0000 | 2.86–3.36 | 0.13 | 0.0000 | 0.11–0.14 |
| Therapist's discipline | 1.28 | 0.0001 | 1.21–1.35 | 1.24 | 0.0001 | 1.11–1.39 | | | |
| Treatment modality | 1.49 | 0.0001 | 1.43–1.55 | | | | | | |

[a] Includes outpatients only; excludes patients seen for assessment purposes only.
[b] Includes outpatients and inpatients; excludes patients seen for assessment purposes only.
[c] Antilog of the regression coefficient.
[d] Odds ratio.
[e] N=4,474 for analysis of setting.
[f] Baseline.
[g] N=4,046 for analysis of setting.
[h] N=3,098 for analysis of setting.
[i] N=3,992 for analysis of setting.

Bivariate analyses based on a larger sample (N=12,889) provided a more detailed description of the relationships between treatment modality and the other variables. To show the significance and magnitude of the association, we used both chi-square and Cramer's V. These analyses supported the regression analysis. All of the other racial/ethnic groups received more treatment that included medication than did whites: 1,430 (39.6%) of the white patients, 1,607 (49.2%) of the black patients, 1,228 (43.4%) of the Latino patients, and 1,447 (45.5%) of the Asian patients received medication ($\chi^2$=66.42, df=3, p=0.000, Cramer's V=0.07). Fewer patients in the lower socioeconomic classification (N=1,356 [43.8%]) than in the higher classification (N=4,348 [46.0%]) received medication. Fewer patients whose primary language was English (N=3,468 [44.3%]) than patients whose primary language was not English (N=1,395 [50.0%]) received medication. More psychotic patients (N=3,261 [57.4%]) than nonpsychotic patients (N=2,450 [34.0%]) received medication.

The third treatment variable studied was the setting of treatment, categorized as inpatient or outpatient. Table 1 displays the relationships of race/ethnicity and five covariates to the setting of treatment. Asian patients were significantly more likely than white patients to be treated in an outpatient setting. Similarly, Latinos were significantly more likely to be treated as outpatients than whites. The relationship of black race/ethnicity to treatment setting was not significant.

Age, sex, and diagnosis had significant relationships to treatment setting; socioeconomic status and primary language did not. Older age and female sex significantly increased the odds of outpatient treatment. Diagnosis had the greatest relationship to treatment setting.

The results of the bivariate analyses of 12,889 outpatients and 6,511 inpatients are described briefly here to provide more detail. More of the blacks (N=2,065 [38.7%]) and fewer of the Latinos (N=1,109 [28.1%]) than whites (N=1,739 [32.5%]) were treated as inpatients ($\chi^2$=117.74, df=3, p=0.000, Cramer's V=0.08). Inpatients were younger than outpatients: 3,653 (56.1%) of the inpatients were in the younger age group (18–30 years), compared with 5,948 (46.1%) of the outpatients ($\chi^2$=213.79, df=3, p=0.000, Cramer's V=0.11). A significantly greater percentage of inpatients (N=3,607 [55.4%]) than outpatients (N=6,138 [47.6%]) were men ($\chi^2$=104.64, df=1, p=0.000, Cramer's V=–0.07). The difference between inpatients and outpatients was greatest when psychotic diagnosis was considered: 5,533 (85.5%) of the inpatients and 5,683 (44.1%) of the outpatients had psychotic diagnoses ($\chi^2$=3024.47, df=1, p=0.000, Cramer's V=–0.40).

The final measure of treatment examined was the therapist's discipline. This variable was categorized as professional or nonprofessional. Therapists in professional disciplines included psychiatrists, psychiatric nurses, psychologists, and social workers. Therapists in nonprofessional disciplines included all other licensed and unlicensed technicians and mental health workers. The relationship of race/ethnicity and five covariates to therapist's discipline are displayed in table 1. Race/ethnicity was not significantly related to the therapist's discipline for any of the racial/ethnic groups. Age and sex were also not significantly related to the therapist's discipline. Socioeconomic status, primary language, and

**TABLE 1 (continued)**

| Relationship to Therapist's Discipline (N=10,599)[a] | | |
|---|---|---|
| Effect[d] | p | 95% Confidence Interval |
| 1.00[f] | | |
| 0.86 | 0.06 | 0.72–1.01 |
| 1.14 | 0.09 | 0.98–1.33 |
| 1.06 | 0.47 | 0.90–1.26 |
| 1.00 | 0.70 | 0.99–1.00 |
| 1.09 | 0.17 | 0.97–1.20 |
| 0.88 | 0.05 | 0.78–1.00 |
| 0.81 | 0.006 | 0.69–0.94 |
| 0.68 | 0.0000 | 0.61–0.76 |

diagnosis were significantly related: patients of low socioeconomic status, whose primary language was English, and whose diagnosis was psychotic were more likely to see nonprofessional therapists. Again, the magnitude of the relationship was greatest for psychotic diagnosis.

For the bivariate analyses, the therapist's discipline was further categorized as psychiatric nurse, psychiatrist, psychologist, social worker, licensed psychiatric technician, unlicensed mental health worker, and others. Most patients (N=10,978 [85%]) were seen by therapists in disciplines designated as professional. Of the patients seen by professionals, social workers saw about 40%, psychiatrists saw about 30%, and psychiatric nurses and psychologists each saw about 15%. These percentages probably reflect the numbers of each of these disciplines working in the Los Angeles County mental health system. The relationship between race/ethnicity and the therapist's discipline was significant ($\chi^2$=393.65, df=18, p=0.000, Cramer's V=0.10). However, the majority of patients in all racial/ethnic groups were seen by social workers and psychiatrists (in that order): 2,070 (57.4%) of the whites, 1,938 (59.3%) of the blacks, 1,831 (57.6%) of the Asians, and 1,856 (65.6%) of the Latinos.

Bivariate analysis revealed that more patients in the higher socioeconomic classification (N=1,670 [56.7%]) were seen by social workers and psychologists and that more patients in the lower socioeconomic classification (N=3,695 [37.2%]) were seen by psychiatrists and licensed psychiatric technicians ($\chi^2$=213.11, df=6, p=0.000, Cramer's V=0.13). The other discipline categories were similar for patients in the two socioeconomic categories. More patients whose primary language was English (N=1,835 [23.4%]) were seen by psychiatric nurses and licensed psychiatric technicians, and more patients whose primary language was not English (N=1,357 [48.6%]) were seen by social workers and unlicensed mental health workers ($\chi^2$=303.97, df=6, p=0.000, Cramer's V=0.17). Finally, more of the psychotic patients (N=3,014 [53.1%]) were seen by psychiatric nurses, psychiatrists, and licensed psychiatric technicians ($\chi^2$=222.49, df=6, p=0.000, Cramer's V=0.13). More nonpsychotic patients (N=3,699 [51.3%]) were seen by psychologists and social workers.

## DISCUSSION

Racial/ethnic group identity was not consistently and significantly related to the four measures of psychiatric treatment examined. However, diagnosis was significantly and consistently related to all four measures of treatment. Furthermore, the magnitude of the relationship of diagnosis to each of the treatment measures was always greater than the relationship of any of the other variables considered in the regression model. In addition, socioeconomic status and primary language each had significant and consistent relationships with the same three treatment measures.

There were significant relationships between racial/ethnic group and some treatment measures. Black race/ethnicity was significantly related to two treatment measures: number of sessions with the primary therapist and treatment modality. Compared with white patients, black patients had fewer sessions with their primary therapist and more treatment with medication. This latter finding is similar to the findings of Dunn and Fahy (3) that blacks were more likely to receive neuroleptics than whites. They related this finding partially to diagnosis, noting that blacks received more diagnoses of schizophrenia than whites.

Asian race/ethnicity was significantly related to two measures of treatment: number of sessions with the primary therapist and setting of treatment. Compared with whites, Asians had more sessions with the primary therapist and were more often treated as outpatients.

Latino race/ethnicity in the present study was significantly related to only one measure of treatment: setting. Latinos were more often treated as outpatients than were whites.

The issue of diagnosis appears to be an important one in the consideration of treatment. In this study, diagnosis had a consistent and highly significant relationship to all measures of treatment. A psychotic diagnosis was significantly related to fewer sessions with the primary therapist, a greater likelihood of being treated with medication, less of a chance of being treated as an outpatient, and less of a chance of being treated by a professional therapist. Although inpatient treatment and medication use might be considered intensive treatments, it might also be said that a diagnosis of psychosis was related to less treatment—fewer sessions with a nonprofessional therapist. Interestingly, low socioeconomic status was also related to fewer sessions with the primary therapist and to being treated by a nonprofessional therapist. Low socioeconomic status was related to less use of treatment with medication as well. These findings might be cautiously interpreted as meaning that patients of lower socioeconomic status received less treatment overall. This interpretation would be consistent with the findings of Mollica and Milic (1), who reported that lower socioeconomic groups received low-intervention treatment from nonprofessionals.

Finally, in the present study, the patient's primary language was significantly related to number of sessions with the primary therapist, treatment modality, and therapist's discipline. Patients whose primary language was English had fewer sessions with their primary therapist, less treatment with medication, and less treatment by a professional therapist. Over 95% of white and black patients spoke English as their primary language, but about half of the Latino patients and 40% of the Asian patients did so.

The findings of this study are limited by its retrospective design and the use of data collected more for clinical than research purposes. However, generalizability is enhanced by the large sample size, the natural setting, and the collection of data over several years from all county mental health facilities. Conclusions and recommendations should be made cautiously.

Two groups of patients were receiving less overall treatment: patients in the lower socioeconomic classification and psychotic patients. An important question for clinicians and researchers to consider in any modification of the service delivery system would be whether the treatment provided to psychotic patients is the treatment of choice in terms of effectiveness. Might services be improved by more contact with the primary therapist and with a professional therapist? The mental health service system needs to find out why there seems to be a bias against the treatment of patients in lower socioeconomic classifications. The relationships of diagnosis and socioeconomic status to treatment demand further study if only to document treatment standards and to raise for discussion how services might be improved.

A second issue for consideration in any modification of the service delivery system has to do with underutilization of services and retention in treatment. Both Asians and Latinos have been reported to underutilize services (7, 9). Blacks have been reported to both underutilize and overutilize services (2, 10). Based on their 1985 proportions in the general population of Los Angeles County and their proportions in the mental health care system, it might be said that blacks (12.8% versus 20.5%) were overutilizing Los Angeles County mental health services, that Latinos (33.7% versus 25.5%) and Asians (8.7% versus 3.1%) were underutilizing services, and that whites (44.2% versus 43.0%) were using services in proportion to their numbers in the general population. Of course, these figures do not take into account the need for services or the use or availability of other service systems.

Blacks, Latinos, and Asians have all been reported to terminate treatment earlier than whites (4, 12, 17). In the present study, 2,855 (93.5%) of the whites, 2,272 (91.0%) of the blacks, 2,206 (95.1%) of the Latinos, and 2,582 (94.6%) of the Asians had two or fewer sessions with their primary therapist. A serious issue that needs to be addressed is education of the community in the use of the service delivery system. A question for further research is whether some racial/ethnic groups are using alternative, informal systems of care.

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# The Relationship Between Community Resources and State Hospital Recidivism

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*Objective: The authors examined the propositions that a revolving state hospital door is an inevitable consequence of deinstitutionalization and that enhancing resources for community-based care can limit this phenomenon. Method: They analyzed the recidivism patterns of state hospital patients in a region of Massachusetts where, because of a federal court consent decree, the level of funding for community programs was more than twice as high as it was in other regions in the state and compared the pattern of recidivism in this region with that observed in the other areas of the state. Results: Despite the fact that the average daily state hospital census in the resource-rich region was only half that of the other regions, longitudinal data on hospital use showed that the readmission patterns were similar in all state regions. Conclusions: The authors suggest that attributes of serious and persistent mental illness may have more effect on hospital readmission patterns than service system variables.*

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It has been said that efforts at mental health reform often resolve one set of problems at the expense of bringing about new ones (1). Over the past three decades the reforms embodied in the process of deinstitutionalization have led to dramatic decreases in the populations of state hospitals. In Massachusetts, for example, this period has seen a reduction in the average daily census of state hospitals by a factor of 10, from roughly 25,500 patients in 1955 to approximately 2,500 in 1985. This time period has also seen the growth of a population of "chronic recidivists" or "revolving door" patients (2–4), whose lifetime admissions may in some cases number more than 100 (unpublished 1990 paper of J.L. Geller).

State hospital recidivists have substituted multiple short hospitalizations for the prolonged inpatient care that was the much-criticized hallmark of institutional psychiatry in the first half of this century (5). However, the "roller coaster" of inpatient treatment, discharge, decompensation in the community, and readmission is of questionable clinical value and may frustrate patients, clinicians, and families in their mutual attempts to achieve effective treatment and stable community placements for individuals with serious and persistent mental illness. Moreover, the intensive use of services by these patients makes them particularly costly to serve (6, 7).

Factors alleged to contribute to the persistence of state hospital recidivism are myriad. Prominent among these are the demographic characteristics of the population, which currently includes large numbers of young patients who are in the most active phase of their serious mental disorders (8), and the inadequacy of most service systems designed to support discharged patients in the community. These inadequacies include insufficient resources for the provision of residential care, day treatment, outpatient therapy, crisis intervention, and case management and the resulting, overwhelming failure to achieve continuity of care (9, 10).

The evolution of deinstitutionalization has spawned two important propositions regarding state hospital recidivism. The first is that striving to serve most individuals with serious and persistent mental illness in the community inevitably triggers a "revolving door" pattern of hospital utilization as a function of the shift in locus of services. The second is that the extent of chronic recidivism in a population is inversely related to the amount of community mental health resources available to that population. Neither proposition has been put to an adequate empirical test.

In this paper we report the outcome of such a test. Our study takes advantage of a natural experiment in deinstitionalization afforded by the consequences of a

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**TABLE 1. Average Per Capita Expenditures for Mental Health Services in Five Massachusetts Department of Mental Health Regions, 1986, 1987, and 1989**

| | Average Per Capita Expenditure (dollars) | | | | | | |
|---|---|---|---|---|---|---|---|
| Service | Region I | Region II | Region III | Region IV | Region V | Regions II–V (weighted average) | Difference Between Region I and All Other Regions (%) |
| Inpatient care | 13.79 | 26.04 | 14.98 | 28.33 | 16.44 | 21.40 | –35.56 |
| Emergency services | 5.60 | 2.43 | 2.36 | 2.20 | 2.49 | 2.35 | 138.30 |
| Residential programs | 17.91 | 4.76 | 4.68 | 4.60 | 4.74 | 4.68 | 282.69 |
| Day treatment | 3.57 | 2.08 | 1.93 | 2.15 | 1.44 | 1.90 | 87.89 |
| Outpatient care | 6.62 | 5.37 | 4.78 | 5.72 | 3.11 | 4.73 | 39.96 |
| Vocational training | 2.19 | 0.91 | 0.11 | 0.72 | 0.38 | 0.50 | 338.00 |
| Support services | 1.72 | 1.52 | 1.75 | 1.22 | 1.00 | 1.35 | 27.41 |
| Case management | 3.81 | 0.67 | 1.47 | 0.90 | 1.28 | 1.11 | 243.24 |
| Administration | 0.92 | 0.45 | 0.30 | 0.51 | 0.42 | 0.42 | 119.05 |
| Total community services | 42.34 | 18.19 | 17.38 | 18.01 | 14.86 | 17.05 | 148.33 |
| Total adult services | 56.13 | 44.23 | 32.36 | 46.34 | 31.31 | 38.45 | 45.98 |

legal intervention in western Massachusetts, the Northampton Consent Decree (11), which came about as the resolution in the lawsuit *Brewster v. Dukakis* (12).

## BACKGROUND

The *Brewster v. Dukakis* suit charged that the right of patients at Northampton State Hospital to be treated in the least restrictive environment was compromised because community services that would facilitate their discharge and their community tenure had not been developed. Under the terms of the Northampton Consent Decree (11) the Commonwealth of Massachusetts was obligated to reduce the census at Northampton State Hospital through the creation of a well-funded and integrated system of community services, including residential programs, day treatment, emergency services, and case management. Compliance with the Northampton Consent Decree has resulted in substantial expenditure of funds for community-based programs in one region of the Massachusetts Department of Mental Health (Region I) over the past 10 years. The other regions of the state, which were not part of the Northampton Consent Decree, have been funded at much lower levels.

It is important to note that the service system created in Region I under the Northampton Consent Decree was not simply the result of increased funding. Its development was the product of a comprehensive planning effort that assessed the needs of patients in Region I and designed specialized residential and support services targeted to meet those needs. In addition, because keeping patients out of the state hospital was a major, if not *the* major focus of the Northampton Consent Decree, resources were committed to the continuum of admission diversion services, including crisis intervention, prescreening, and respite care. These services facilitated short-term intervention in a supervised setting outside of the hospital.

The regional differences in resources arising from the Northampton Consent Decree have been striking. The data in table 1 show *actual* per capita expenditures (as opposed to budgetary projections) for a range of community services across five regions of the Massachusetts Department of Mental Health averaged for fiscal years 1986, 1987, and 1989 as well as the average, weighted by population, of expenditures in Regions II, III, IV, and V. (An additional region, Region VI, which includes the metropolitan Boston area, has been omitted from the analysis because the structure of its service delivery system and the context in which services are delivered are considerably different from all of the other regions.) The data given in table 1 indicate that the average for total community resources in Region I was 148% greater than the average in Regions II, III, IV, and V. It also shows that in the categories of residential programs, vocational training, and case management the differences between Region I and the other regions approached or exceeded 250%. Also noteworthy is the fact that the difference in per capita expenditures for total community resources between the best and the least well-funded regions other than Region I—Regions II and V, respectively—was only 22%. This relative homogeneity across Regions II–V with regard to funding supports their use as comparison groups for Region I, both individually and as a group.

In terms of actual services delivered, these differences mean, for example, that Region I had 109 intensively staffed residential placements, while the adjacent region, Region II, had none. Likewise, Region I had a larger complement of case managers, which means that the caseload per worker (16.5 patients) was 32% below the statewide average.

It is important to note that these extreme differences in resource levels were not observed across all service categories. In particular, the difference between Region I and the other regions in expenditures for outpatient care was relatively small given the difference in the sizes of the deinstitutionalized populations across regions (table 1).

The effects of this unequal distribution of resources on different aspects of the state hospital have been previously reported in the *Journal* (13, 14). However, because these utilization patterns provide an important backdrop for the assessment of recidivism, we briefly summarize them here.

During the first 8 years the Northampton Consent Decree was in effect, the average daily census at Northampton State Hospital declined by 46%, compared with only a 16% decline in the remainder of the system. Likewise, rates of first and total admissions to Northampton State Hospital dropped by 46% and 40%, respectively, but actually increased elsewhere in Massachusetts. These trends suggest that the enhancement of the community system did make a substantial contribution to reducing the use of the state hospital, although not as great as envisioned in the original Northampton Consent Decree plan. Closer analysis of the nature of this decline, however, shows that the reduction in census was not uniform across the spectrum of patients. A comparison of the characteristics of the inpatient populations at Northampton State Hospital with a another state hospital (Worcester State Hospital) serving a similar contiguous region on sample days in 1977 (before the Northampton Consent Decree's effective date of December 7, 1978) and 1986 showed that the major differences between these two hospitals on the latter date lay in their long-stay populations. The acutely ill patients at Northampton State Hospital (those who had been hospitalized for 90 days or less on the day of assessment) were less affected by the Northampton Consent Decree and, although fewer in number, did not differ in terms of their diagnostic or demographic characteristics from the acutely ill patients at Worcester State Hospital (13).

Northampton State Hospital continues to be used far less than other state hospitals in Massachusetts. In 1989, the average daily census at Northampton State Hospital was 0.21 per 1,000 persons over age 19, less than half the statewide average of 0.51. Moreover, analysis of regional patterns of utilization of all forms of psychiatric inpatient care indicates that the use of general hospital and private psychiatric hospital services was no higher in Region I than in other regions (15), although access to such providers for the Region I population is roughly equivalent to that in the rest of the state.

These data indicate that, on any given day, a larger proportion of the seriously mentally ill population in Region I is being served outside of a hospital setting than is the case elsewhere. This, together with the nearly 150% difference in community resources between Region I and the other regions, affords us the opportunity to examine questions regarding community placement, resource levels, and recidivism in a quasi-experimental framework (16) in which Region I serves as the principal study group and Regions II–V serve as comparison groups.

## METHOD

Using the quasi-experimental design described we implemented two types of analysis. The first was survival analysis, a technique that has been shown to be useful in longitudinal studies of hospital readmission patterns in which some subset of the patients under study are likely not to be readmitted during the observation period (17). Using the survival functions generated by this method, we compared the community tenure (defined for our purposes as the length of time between discharge from and readmission to a state inpatient facility) of patients discharged from Northampton State Hospital in Region I between July 1, 1985, and June 30, 1986, with patients discharged from state inpatient facilities in Regions II, III, IV, and V over the same time period. The endpoint of the observation period was June 30, 1989. The null hypothesis that the survival functions would be equivalent across regions was tested by using the Lee-Desu statistic (18).

Survival analysis is useful in showing the probabilities associated with community tenures of varying length and in allowing these probabilities to be compared across regions. However, it does not fully capture the intensity with which inpatient care is used. To address this facet of the recidivism phenomenon we conducted a second analysis that drew on the utilization patterns of the patients using state inpatient facilities in the five areas over the period 1986–1989. Using these data, we compared the proportion of patients experiencing one, two, three, or more admissions over the 4-year period in each region. We should clarify that these data are based on the utilization patterns of all patients admitted to Massachusetts state hospitals in Regions I–V over a 4-year period. Patients admitted in the second, third, and fourth years would not have been "at risk" for as many admissions during the observation period as those admitted in the first year, however, and our estimates of the prevalence of chronic recidivism, therefore, may be low. This factor does not, of course, affect our between-region comparisons because the same measurement procedures were used for all patients.

## RESULTS

The survival functions estimated for each of the regions are shown in table 2. The values of these functions represent the probability of remaining in the community (i.e., outside of the state hospital) for a length of time equal to the interval specified (e.g., 30 days, 90 days). These data indicate that the likelihood of prompt readmission in all regions was substantial. Across the five regions the probability of readmission within 30 days was between 11% and 20%; the probability of readmission within 60 days was between 16% and 26%. The majority of patients experienced prolonged tenure, however; in all but one region (Region II), the probability of remaining outside a state facility for 4 years after discharge was about 50%.

To test the hypothesis that the community tenure of Region I patients was different from that of patients in the other four regions, we compared survival functions across regions. A comparison of the survival function

**TABLE 2. Community Tenure Probabilities for Patients Discharged From Inpatient Facilities in Five Massachusetts Department of Mental Health Regions Between July 1, 1985, and June 30, 1986**

| | Probability of Remaining in the Community | | | | |
|---|---|---|---|---|---|
| Number of Days After Discharge | Region I (N=624) | Region II (N=889) | Region III (N=1,121) | Region IV (N=1,732) | Region V (N=1,244) |
| 30 | 0.89 | 0.80 | 0.89 | 0.89 | 0.87 |
| 60 | 0.84 | 0.74 | 0.83 | 0.83 | 0.83 |
| 90 | 0.81 | 0.70 | 0.80 | 0.80 | 0.80 |
| 180 | 0.73 | 0.63 | 0.72 | 0.72 | 0.73 |
| 270 | 0.68 | 0.58 | 0.66 | 0.67 | 0.68 |
| 360 | 0.64 | 0.54 | 0.63 | 0.64 | 0.65 |
| 540 | 0.58 | 0.51 | 0.58 | 0.61 | 0.60 |
| 720 | 0.54 | 0.47 | 0.55 | 0.58 | 0.56 |
| 1,080 | 0.51 | 0.44 | 0.51 | 0.56 | 0.52 |
| 1,440 | 0.48 | 0.41 | 0.49 | 0.54 | 0.51 |

in Region I with those calculated for each of the other regions showed that only one region, Region II, had significantly different community tenure (Lee-Desu statistic=16.84, df=4, p=0.0000). In fact, Region II patients had significantly lower community tenure probabilities than those in all other regions. No other comparisons with Region I were statistically significant, and when Regions II–V were combined and the survival function for the combined group was compared with that for Region I the difference was not statistically significant (Lee-Desu statistic=0.21, df=1, p=0.65).

The impression that the regions differed little with regard to community tenure and, therefore, in the extent of chronic recidivism, was reinforced when we compared the distribution of the number of admissions experienced by all Northampton State Hospital patients and all those using Massachusetts Department of Mental Health facilities in the four comparison regions (N=14,522) between 1986 and 1989. As shown in figure 1, the distribution of admissions across regions was virtually identical. In fact, the proportion of patients exhibiting the most intense hospital utilization over this period—those with seven or more admissions—actually varied relatively little across regions but was slightly higher in Region I (3.3%) than the average for all of the other regions (2.4%).

## DISCUSSION

The findings reported here, obtained from two perspectives on hospital readmission patterns, reveal little difference between Region I and the four comparison regions with regard to recidivism patterns. This finding occurred despite the nearly 100% difference in the extent of deinstitutionalization and the 148% difference in levels of community resources between Region I and Regions II, III, IV, and V.

Findings that two groups did not differ significantly are often regarded as uninteresting and/or not worth reporting. However, outcomes that are clearly inconsistent with policy objectives warrant attention and discussion. These data indicate that a difference of more than 100% in the proportion of the population served in the community did not lead to an accelerated revolving door in Region I because, we might assume, more than twice as many community resources were available and delivered here than in the other regions. At the same time, the availability of these resources did not eliminate the "revolving door" population: these patients made up similar percentages of the hospital-using populations in Regions I, II, III, IV, and V.

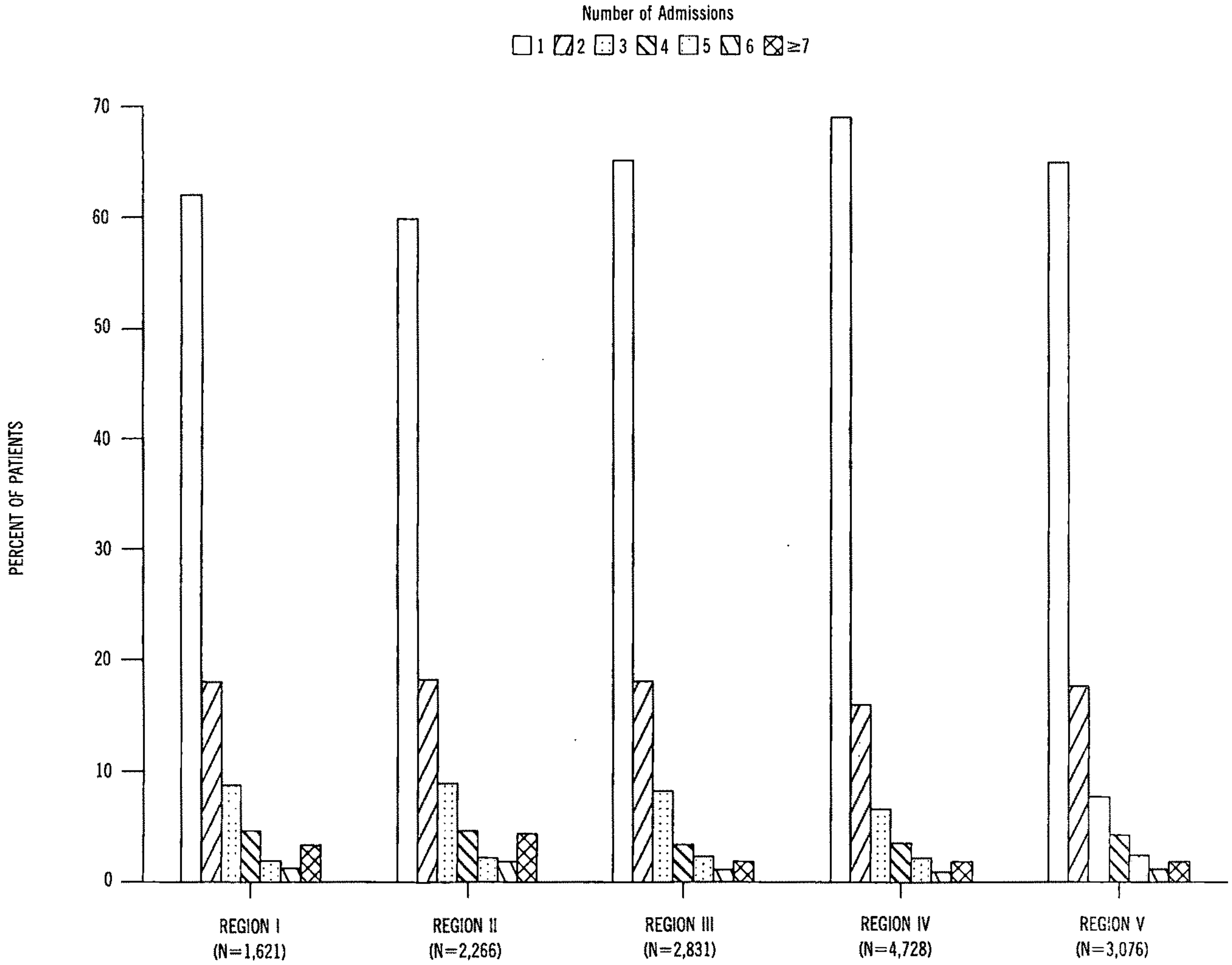
These data argue that large numbers of individuals with serious and persistent mental illness can be served in the community without developing a disproportionately large chronically readmitted population if a comprehensive array of services is made available to them. The data also indicate, however, that the problem and pattern of chronic recidivism is similar in catchment areas with comprehensive services and in catchment areas where services are not so plentiful.

Why is this the case? Our data do not allow us to answer this question directly, but generating some hypotheses should be useful for guiding further investigation.

One possible explanation is that the design of the community service system in Region I is flawed. The infusion of resources for residential programs in Region I has shifted where people live—from the hospital to the community. The emphasis on housing and the relative lack of emphasis on assertive community treatment, however, a pattern seen all too often in community service systems (10), has not prevented hospitalization and rehospitalization for some patients with serious mental disorders. The service system in Region I has been highly effective in reducing the size of Northampton State Hospital's long-stay population and has eliminated some groups of patients (e.g., psychogeriatric patients) from the hospital altogether (19). But a model so heavily focused on the residential resources required for community placement may be ill-equipped to cope with the exacerbations of acute illness and the treatment needs of chronic illness. Indeed, the low level of funding for outpatient treatment in Region I relative to that for other types of service may be indicative of this problem.

A second hypothesis is that the allocation of resources across the community service system is sound but the execution is flawed. We have neither empirical nor anecdotal data to support this proposition, how-

FIGURE 1. Number of Hospital Admissions per Patient in Five Regions of the Massachusetts Department of Mental Health, July 1, 1986–June 30, 1989



ever. Whether different organizational and administrative arrangements, such as an effective central mental health authority (20), would promote more effective service delivery remains to be tested. Also worthy of consideration is the impact of outpatient commitment in this type of resource-rich environment. Although Massachusetts has not statutorily defined outpatient commitment, variants of this intervention have been used in Massachusetts by applying the emergency detention provision of the commitment law (21) and probate court substituted-judgment decisions (22). It is noteworthy that these procedures have been used much more extensively in Region I than elsewhere in the state. How involuntary community treatment and community expenditures for services interact has been discussed (23, 24) but not yet systematically studied.

A third hypothesis postulates the existence of a population of patients in all regions who need inpatient treatment at different times. In Region I these individuals experience trials of community placement as well as frequent readmissions, but their counterparts in other regions are hospitalized for longer periods of time, experiencing fewer trials in the community because of the absence of community programs to support them. Longer stays in the hospital with fewer trials in the community result in fewer state hospital admissions but more hospital days. This would explain the slightly higher rate of recidivist admissions in Region I than in some of the other regions. On the other hand, the level of recidivism reported here may inadequately reflect the true recidivism pattern due to the considerable availability of admission-diversion beds in Region I and the relative lack of these resources in other regions.

This hypothesis focuses on the nature of serious and persistent mental illness per se. We may be observing relapse patterns that have more to do with variations in the clinical course of serious mental disorders than with the nature of the services patients receive. To the extent that this is the case, this needs to be explicitly recognized in any service system design. This view also shifts the basis for clinical care and treatment back to the nature of the illness itself and away from the alleged pervasive effects of institutionalism (25, 26).

A fourth hypothesis focuses on case finding. It may be that comprehensive community service systems, where most patients have case managers and many live in some form of residential program, identify patients in need of hospitalization more quickly and more often than do those in which patients are less carefully followed. If this is the case, it might be that fewer of the repeat admissions in Region I than in Regions II–V were what some providers call "inappropriate admissions." This would be consistent with arguments claiming that many state hospital admissions are clinically justifiable and not indicative of programmatic failure (27).

The data presented here were derived from comparisons involving one model of delivering community-based care—one that strongly emphasizes residential programming. There are others in place around the United States that emphasize alternative approaches, such as intensive case management or assertive community treatment (28). A great deal can be learned about the fundamental suppositions of community mental health through examining and comparing the experiences, clinical status, and quality of life of individuals functioning within these different models of care and treatment. Such comparisons, drawing on "experiments" in service delivery, court-ordered service expansion, "model programs," and other interventions leading to major alterations in service systems, should help us better understand what patients, families, and providers can and cannot expect from different approaches to serving the seriously and persistently mentally ill in the community.

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# Vitamin E in the Treatment of Tardive Dyskinesia: A Double-Blind Placebo-Controlled Study

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*The authors compared vitamin E with placebo in a double-blind randomized crossover study of 27 patients with tardive dyskinesia. Each treatment period lasted for 6 weeks. Vitamin E showed no differences from placebo in the treatment of tardive dyskinesia.*

(Am J Psychiatry 1992; 149:391–393)

A rationale for using antioxidants, such as vitamin E, in the treatment of tardive dyskinesia has been put forth (1–3), and two clinical trials have found vitamin E to be effective in decreasing the severity of tardive dyskinesia (1, 3). Our aim in this study was to replicate the short-term effectiveness of vitamin E in the treatment of tardive dyskinesia in a larger group of patients.

## METHOD

Twenty-seven outpatients (17 women and 10 men), 18 to 70 years old, were included in the study. These patients met Research Diagnostic Criteria for at least mild tardive dyskinesia (4), had stable psychopathology, and had been on a stable psychotropic drug regimen for at least 2 months before study entry. Twenty-two of the patients met *DSM-III-R* criteria for schizophrenia, and five met *DSM-III-R* criteria for bipolar disorder. All subjects provided signed informed consent.

The mean age of the patients was 42.9 years (SD=12.6, range=19–69). Twenty-one were receiving injectable neuroleptics, five were receiving oral neuroleptics, and one was not receiving any neuroleptic. Twenty (74%) of the patients had been ill for longer than 10 years and had been receiving neuroleptic drug therapy for a similar period.

The study design was double-blind and placebo-controlled and included a randomized crossover of two 6-week treatment periods with either vitamin E or placebo. The first treatment period was followed by a 2- or 3-week placebo washout period depending on the length of each subject's depot neuroleptic interval.

During treatment periods, vitamin E or placebo was administered on a fixed dosage schedule of one capsule of 400 IU of vitamin E or a placebo of identical appearance three times a day. During the placebo washout period, a placebo capsule was administered three times a day. To monitor compliance, capsule count was verified at each visit. Doses of all psychotropic medication were kept unchanged throughout the study.

All patients were assessed by the same investigator (C.L.S.), who used the Abnormal Involuntary Movement Scale (AIMS) (5) and the Extrapyramidal Symp-

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**TABLE 1. Extrapyramidal Symptom Ratings of 27 Patients Before Treatment and at Termination of Vitamin E and Placebo Treatments**

| | Baseline | | Vitamin E | | Placebo | | Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Scale | Mean | SD | Mean | SD | Mean | SD | Mean[a] | SEM | t (df=25) | p[b] |
| Extrapyramidal Symptom Rating Scale subscales | | | | | | | | | | |
| Parkinsonism, dystonia, and dyskinesia questionnaire | 3.30 | 2.89 | 2.19 | 1.30 | 2.07 | 1.66 | –0.15 | 0.30 | 0.50 | 0.62 |
| Parkinsonism: physician's examination | 7.85 | 4.96 | 5.70 | 5.68 | 6.63 | 5.43 | –1.17 | 1.07 | 1.09 | 0.29 |
| Dystonia: physician's examination | 1.07 | 1.59 | 0.93 | 1.30 | 0.59 | 0.75 | 0.31 | 0.24 | 1.28 | 0.21 |
| Dyskinetic movements: physician's examination | 13.89 | 4.56 | 9.85 | 5.70 | 10.19 | 4.66 | –0.31 | 1.00 | 0.31 | 0.76 |
| Clinical global impression of severity of dyskinesia | 3.41 | 1.12 | 2.63 | 0.84 | 2.78 | 0.89 | –0.15 | 0.13 | 1.15 | 0.24 |
| Clinical global impression of severity of parkinsonism | 0.96 | 1.26 | 0.93 | 1.11 | 1.04 | 1.06 | –0.18 | 0.24 | 0.72 | 0.48 |
| AIMS | 8.52 | 3.67 | 7.11 | 4.27 | 7.11 | 3.61 | –0.05 | 0.55 | 0.09 | 0.93 |

[a] Least squares estimate from analysis of variance for two-period crossover design. The least squares estimate is adjusted for the fact that the number of patients beginning treatment with vitamin E differed from the number beginning treatment with placebo.
[b] Two-tailed.

tom Rating Scale (6) at baseline and every 2 or 3 weeks thereafter (depending on the injection schedule of each patient receiving depot neuroleptics) until the completion of the study. Placebo-drug differences were examined with repeated-measures analysis of variance (ANOVA) for a two-period crossover design as described by Fleiss (7).

## RESULTS

Repeated-measures ANOVA for the two-period crossover design revealed no significant differences ($p<0.05$, two-tailed) or trends ($p<0.10$) between vitamin E and placebo treatment with respect to the endpoint mean scores for the Extrapyramidal Symptom Rating Scale subscales or the AIMS total score, as shown in table 1. Similarly, analysis of the individual items of the Extrapyramidal Symptom Rating Scale dyskinetic movements subscale revealed no significant differences ($p<0.05$) or trends ($p<0.10$) between the treatments, ruling out effects on specific body areas. On the AIMS total score there were statistically significant but clinically modest reductions from baseline mean scores following both vitamin E and placebo treatment (table 1).

Statistical power calculations (8) revealed that the number of patients studied (N=27) provided 80% power to detect a true difference between treatment and placebo of 22.5% in AIMS total scores and 29.5% in the Extrapyramidal Symptom Rating Scale dyskinetic movements subscale scores ($p<0.05$, two-tailed).

## DISCUSSION

The results of this study suggest that the short-term use of 400 IU of vitamin E three times a day conferred no advantage over placebo in the treatment of tardive dyskinesia in this group of patients, the majority of whom had been treated with neuroleptic drugs for more than 10 years. The modest reductions from baseline in dyskinetic movements that occurred at the end of treatment with both vitamin E and placebo may have been related to decreased stress levels that occurred when patients became more familiar with the experimental procedures. It is well-known that tardive dyskinesia can be exacerbated by stress.

Our finding may represent differences between our patients and the subjects of two previous studies in which vitamin E showed a significant effect over placebo (1, 3). First, our patients had a long exposure to neuroleptics and had had tardive dyskinesia for several years. This factor could have reduced the effectiveness of vitamin E because patients without a lengthy exposure to neuroleptics and a relatively short onset of tardive dyskinesia (e.g., less than 2 years) may be the patients most likely to benefit from antioxidative therapy. Second, most of the patients in our study were receiving injectable neuroleptics and were regularly assessed just before their next neuroleptic injection. The timing of assessments of tardive dyskinesia may have added a withdrawal-emergent component for which vitamin E is of little or no benefit. Third, a possible drug interaction between vitamin E and injectable neuroleptics, which undergo a different hepatic metabolism from oral neuroleptics, was not examined in the context of this study. Finally, the placebo effect observed has been reported in other studies of tardive dyskinesia (9), suggesting that psychological and nonspecific factors may affect the course of a controlled clinical trial.

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# Alcohol Abuse, Depression, and Suicidal Behavior in Schizophrenia

Stephen J. Bartels, M.D., Robert E. Drake, M.D., Ph.D., and Gregory J. McHugo, Ph.D.

*Alcohol use was correlated with depression and suicidal behavior in two independent studies of schizophrenic outpatients. Depression alone accounted for over 80% of the explained variance in suicidal behavior in both studies; alcohol use alone and the correlation between depression and alcohol use accounted for only small amounts of variance.*

(Am J Psychiatry 1992; 149:394–395)

People with primary alcohol use disorders are highly likely to suffer from depression and suicidal behavior (1, 2). Alcohol appears to induce suicidal behavior through both its depressant and its disinhibitory effects. Schizophrenic patients also have high rates of alcohol abuse (3, 4), depression (5), and suicidal behavior (6). The relationship between depression and suicide in schizophrenia is well documented (6, 7), but, to our knowledge, no one has examined the relationship between alcohol use and depression and suicide in schizophrenic patients. We have therefore addressed this question by examining the data derived from earlier studies of an urban group and a rural group of outpatients with schizophrenia.

## METHOD

Subjects in the study of urban patients with schizophrenia were outpatients of a teaching hospital in Cambridge, Mass. (3). Of the 133 patients in this study, 115 had a *DSM-III* diagnosis of schizophrenia and 18 had a *DSM-III* diagnosis of schizoaffective disorder. Their mean age was 38.3 years (SD=11.4). Seventy-eight (59%) were men and 55 (41%) were women. Subjects in the study of rural patients with schizophrenia were outpatients treated in a community mental health center in rural New England (4). These patients were evaluated extensively for alcohol use disorder. Of the 75 patients in this study, 67 had a *DSM-III-R* diagnosis of schizophrenia and eight had a *DSM-III-R* diagnosis of schizoaffective disorder. Their mean age was 43.6 years (SD=14.3). Thirty-six (48%) were men and 39 (52%) were women.

In both studies, primary clinicians rated depression and suicidal behavior (suicidal ideation or suicide attempts) on 5-point scales on which 1=not present, 2=mild, 3=moderate, 4=severe, and 5=extremely severe. Descriptive anchor points for this scale were based on assessments of symptoms over the preceding 6 months (3). For example, moderate depression was defined by pervasive despondency of mood and moderate suicidal behavior was defined by substantial preoccupation or attempts. Interrater agreement on 18 patients from the urban study, determined by comparing ratings of the clinician and the medication group psychiatrist, were 0.61 for depression and 0.82 for suicidal behavior (Cohen's kappa).

In both studies (3, 4), primary clinicians rated alcohol use over the preceding 6 months on the basis of separate 5-point scales. The clinicians' ratings of current alcohol use, based on longitudinal observations of behavior as well as collateral reports and self-reports, correlated highly with *DSM-III-R* diagnoses of alcohol use disorder made by using structured interviews (4). Interrater reliabilities for the clinicians' ratings in the two studies, determined by comparing ratings of the primary clinicians and medication group psychiatrists, were 0.80 for the urban group and 0.88 for the rural group (Cohen's kappa) (3).

## RESULTS

Current alcohol use disorders (abuse or dependency, determined by a rating of 3 or greater on the clinicians' rating scale) were present in the same proportion (24%) of both the urban and rural studies (32 of the 133 urban patients and 18 of the 75 rural patients). Almost half (47% [N=63]) of the patients in the urban study and almost one-third (32% [N=24]) of the patients in the rural study were rated by clinicians as moderately to extremely depressed. Thirty percent (N=40) of the patients in the urban study and 8% (N=6) of the patients in the rural study were rated by clinicians as moderately to extremely suicidal. There were no completed suicides at the time of evaluation.

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In both studies, alcohol use was correlated with depression (for the urban patients, r=0.19, N=133, p=0.01; for the rural patients, r=0.20, N=75, p<0.05) and with suicidal behavior (urban, r=0.18, p<0.05; rural, r=0.22, p<0.05). Correlations between depression and suicidal behavior were much stronger: r=0.43 (p<0.001) for the urban patients and r=0.51 (p<0.001) for the rural patients.

Commonality analysis was used to determine the relative contribution of depression and alcohol use in explaining the variability in suicidal behavior in both studies. This procedure partitions the explained variance ($R^2$) in the criterion variable (suicidal behavior) into those proportions due uniquely to each predictor variable (depression and alcohol use) and due to the common variance in the predictor variables (8). Table 1 shows that 19% of the variance in suicidal behavior in the study of urban patients and 28% of the variance in suicidal behavior in the study of rural patients was explained by depression and alcohol abuse. For both studies, more than 80% of the explained variance in ratings of suicidal behavior (for the urban group, 84% [0.16 divided by 0.19], for the rural group, 82% [0.23 divided by 0.28]) was accounted for by depression. A considerably smaller percentage (for the urban group, 11% [0.02 divided by 0.19], for the rural group, 14% [0.04 divided by 0.28]) of the explained variance was due to the correlation between ratings of depression and alcohol use, and alcohol use alone accounted for only 5% of the explained variation in ratings of suicidal behavior (for the urban group, 5% [0.01 divided by 0.19], for the rural group, 4% [0.01 divided by 0.28]).

**TABLE 1. Commonality Analysis of the Proportion of Variance in Suicidal Behavior Explained by Depression and Alcohol Use for Outpatients With Schizophrenia in Urban and Rural Settings**

| | Proportion of Total Variance | |
|---|---|---|
| Variance Component | Urban Patients (N=133) | Rural Patients (N=75) |
| Depression | 0.16 | 0.23 |
| Alcohol use | 0.01 | 0.01 |
| Depression and alcohol use | 0.02 | 0.04 |
| Total explained variance ($R^2$) | 0.19 | 0.28 |

## DISCUSSION

These findings indicate that clinicians' ratings of alcohol use in schizophrenic patients have little value in accounting for suicidal behavior beyond that due to depression ratings. In both an urban and a rural group of outpatients with schizophrenia, alcohol use was significantly related to depression and suicidal behavior, but the correlations were small. Most of the explained variance in suicidal behavior was due to depression; only small amounts were explained by alcohol use alone and by the variance common to depression and alcohol use. However, since alcohol use and depression together accounted for only 19% of the total variation in clinicians' ratings of suicidal behavior for the urban patients and only 28% for the rural patients, other factors such as hopelessness may be of greater importance (9, 10).

In interpreting the data, several caveats are in order. First, the two studies used small study groups and the results are therefore tentative, although their consistency across independent rural and urban groups suggests validity. Second, the clinicians' ratings were not independent but had the advantage of characterizing behaviors and symptoms by aggregating observations over time and setting (4). Third, the results are limited by the lack of a comparison study group, but data for nonschizophrenic patients (2) indicate that patients with co-occurring alcohol abuse and depressed mood have an exceptionally high risk for suicide. Fourth, depression in these studies referred to persistent depressed mood rather than major depressive episode. Finally, suicidal behavior in these studies referred only to ideation and attempts. However, our previous study of schizophrenic patients who completed suicide (7) also found a strong relationship between depression and suicide and a weak relationship between substance abuse and suicide.

A strong relationship between alcohol use and suicidal behavior in schizophrenia was not supported by the data. One possible explanation is that because schizophrenic patients often develop alcohol-related problems with less alcohol use than patients with primary alcoholism, alcohol use by schizophrenic patients may be less likely to induce depression and suicidal behavior (4). Clinicians monitoring primary risk factors for suicidal behavior in schizophrenic patients should focus on depression and other clinical correlates that substantially outweigh any contribution of alcohol abuse.

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# Suicidality and HIV Status

F. Patrick McKegney, M.D., and Mary Alice O'Dowd, M.D.

*Among psychiatric consultation patients, 322 AIDS patients were significantly less suicidal than 82 other HIV-positive patients and were comparable in suicidality to 1,086 patients with negative or unknown HIV status. AIDS patients had significantly more organic mental disorders. Organicity, denial, acceptance, and/or preoccupation with a fatal illness may reduce suicidality in AIDS patients.*

(Am J Psychiatry 1992; 149:396–398)

The prevalence of suicidality associated with HIV infection and with progression of HIV-related diseases has been variously reported. Some studies (1, 2) have shown the suicide risk of patients with HIV infection to be 35 to 40 times as high as that of HIV-negative persons. Others (3–5) have reported much lower risk rates, comparable to those found in non-HIV-infected populations. These large discrepancies may be due to differences in the risk groups studied, the stage of HIV-related illnesses, socioeconomic factors, or other sampling biases.

Some research (3, 6) has suggested differences among HIV-infected populations; AIDS patients have shown less emotional distress and suicidality than asymptomatic and symptomatic HIV-positive patients, i.e., those with Centers for Disease Control (CDC) stages I to IVa. We undertook the present study to examine the relationship between suicidality and HIV infection in its various stages; these results have been summarized elsewhere (7).

## METHOD

Data on all patients seen in psychiatric consultation in an 800-bed general hospital were gathered prospectively. The data used in the analysis were for all adult patients aged 55 and under who were seen in three years, 1988–1990. This age limit encompassed all HIV-positive patients and provided a comparably aged group of patients who were either HIV negative or, for the vast majority of patients, of unknown HIV status. It was not possible to assess patients not referred for consultation, but approximately 17% of the AIDS patients admitted were seen in consultation.

Three groups of patients were defined: 1) patients clinically diagnosed as having AIDS (CDC stages IVb to IVe), 2) other HIV-positive patients (CDC stages I to IVa), with or without symptoms, and 3) patients who were known to be HIV negative or whose HIV status was unknown.

As shown in table 1, the AIDS patients and other HIV-positive patients did not differ significantly in sex distribution or racial/ethnic makeup. Both groups were predominately male and Hispanic and significantly different from the group with negative or unknown HIV status. The mean ages of the three groups were 36.5 (SD=8.2), 34.3 (SD=7.1), and 33.9 (SD=13.5) years, respectively; the difference was not statistically significant.

The AIDS patients were significantly sicker than the other two groups; the mean Karnofsky scores of the AIDS patients, other HIV-positive patients, and patients with negative or unknown HIV status were 4.7 (SD=1.9), 5.8 (SD=2.3), and 5.6 (SD=2.2) (ANOVA; F=19.1, df=1, 337, $p<0.001$). (On the Karnofsky scale, 10=well, 0=death; 4.0="Disabled; requires special care and assistance," 5.0="Requires considerable assistance and frequent medical care.")

The 322 AIDS patients were primarily hospitalized for serious complications of AIDS, usually infectious or neurological. Almost one-half of the 82 non-AIDS HIV-positive patients were admitted for bacterial pneumonias, and the remainder were hospitalized for a wide range of non-HIV-related conditions. The admitting diseases of the 1,086 patients with negative or unknown HIV status were cardiovascular (25%), neurological (22%), pulmonary (20%), cancer (18%), gastrointestinal (8%), and renal (12%) (some patients were admitted for more than one disease).

Suicidality was determined on the basis of semistructured clinical interviews, and the same criteria for suicidality were applied to all patients seen in consultation. Virtually all patients were seen by and had their charts

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**TABLE 1. Sex and Ethnicity of AIDS Patients, Other HIV-Positive Patients, and Patients With Negative or Unknown HIV Status Seen for Psychiatric Consultation**

| | AIDS Patients (N=322) | | Other HIV-Positive Patients (N=82) | | Patients With Negative or Unknown HIV Status (N=1,086) | |
|---|---|---|---|---|---|---|
| Variable | N | % | N | % | N | % |
| Sex[a] | | | | | | |
| Male | 209 | 65 | 56 | 68 | 434 | 40 |
| Female | 113 | 35 | 26 | 32 | 652 | 60 |
| Ethnicity[b] | | | | | | |
| Hispanic | 159 | 49 | 41 | 50 | 293 | 27 |
| Black | 112 | 35 | 25 | 30 | 370 | 34 |
| White | 51 | 15 | 16 | 20 | 402 | 37 |

[a] $\chi^2=69.3$, df=2, $p<0.0001$. Significant difference between patients with negative/unknown status and each of the other two groups.
[b] $\chi^2=78.8$, df=4, $p<0.0001$. Significant difference between patients with negative/unknown status and each of the other two groups.

**TABLE 2. Psychiatric Problems in AIDS Patients, Other HIV-Positive Patients, and Patients With Negative or Unknown HIV Status Seen for Psychiatric Consultation**

| | AIDS Patients (N=322) | | Other HIV-Positive Patients (N=82) | | Patients With Negative or Unknown HIV Status (N=1,086) | | Chi-Square Analysis | |
|---|---|---|---|---|---|---|---|---|
| Psychiatric Problem | N | % | N | % | N | % | $\chi^2$ (df=2) | p |
| Suicidality | | | | | | | | |
| Judgment of referring physician | 35 | 11 | 18 | 21 | 114 | 10 | 8.29 | 0.02[a] |
| Judgment of psychiatrist | 29 | 9 | 15 | 18 | 98 | 9 | 6.34 | 0.04[a] |
| Delirium | 139 | 43 | 24 | 29 | 274 | 25 | 36.76 | <0.0001[b] |
| Dementia | 89 | 28 | 9 | 11 | 96 | 9 | 67.15 | <0.0001[b] |
| Substance abuse disorder | 135 | 42 | 42 | 51 | 217 | 20 | 88.87 | <0.0000[c] |
| Adjustment disorder | 115 | 38 | 23 | 28 | 341 | 31 | 3.48 | n.s. |

[a] Significant difference between other HIV-positive patients and each of the other two groups.
[b] Significant difference between AIDS patients and each of the other two groups.
[c] Significant difference between patients with negative/unknown HIV status and each of the other two groups.

reviewed by senior attending psychiatrists (F.P.M., M.A.O.).

Comparisons of the three HIV groups in terms of psychiatric diagnoses and suicidality were made by analysis of variance or chi-square analysis.

## RESULTS

As shown in table 2, the percentage of patients who were considered suicidal by the referring physicians was significantly higher for the HIV-positive patients who had not yet developed AIDS than for the other two groups. The percentage of patients who were determined to be suicidal by psychiatrists was also significantly higher for this group than for the other two groups.

A significantly higher proportion of AIDS patients than patients in the two age-matched comparison groups had delirium and dementia. No significant differences were found in other major psychiatric diagnoses, including affective disorders, except for a lower frequency of substance abuse in the group with negative or unknown HIV status.

## DISCUSSION

These results confirm data gathered in a similar group of subjects (6), who were predominantly intravenous drug users and their sex partners. These data indicate a lower frequency of suicidality and other manifestations of psychological distress in patients with AIDS than in HIV-positive non-AIDS patients. However, the factors contributing to these differences are not clear. The strikingly greater prevalence of delirium and dementia due to HIV, opportunistic infections, and other systemic illnesses suggests that organicity may enhance the use of denial, an association which has been reported over several decades (8).

Another factor contributing to less psychological distress in AIDS patients may be the phenomenon Yalom and Greaves (9) called "cancer cures psychoneuroses." Describing patients who become aware of having cancer or other progressively terminal illnesses, these authors suggested that "facing and mastering some of their fear of death dissolves many other fears . . . . As one's focus turns from the trivial diversions of life, a fuller appreciation of the elemental factors in existence may emerge" (9). In addition, the certainty of an AIDS diagnosis may lead to the development of an attitude of "acceptance" (10), which may reduce psychological distress and suicidality.

Our experience with AIDS and other HIV patients is only beginning, and much more needs to be learned about the presentation of psychological symptoms over the course of the illness. This pilot survey needs replication and amplification.

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# Blood Levels and Acute Response to Bupropion

Paul J. Goodnick, M.D.

*Twenty-three patients with major depressive disorder were treated with bupropion in an open-design protocol. Fifteen (65.2%) of the 23 responded with a more than 50% decrease in scores on the Beck Depression Inventory. Patients with trough blood levels of 10–29 ng/ml had a significantly better response than those with trough levels of 30 ng/ml or more. This preliminary result warrants further, double-blind evaluation.*

(Am J Psychiatry 1992; 149:399–400)

The use of blood levels of antidepressants to maximize efficacy of treatment has long been established (1). Bupropion is a recently released antidepressant whose mechanism of action is unknown, but it may block dopamine re-uptake and act as a partial dopamine agonist (2). It appears to be particularly effective in hypersomniac, hyperphagic unipolar depression and in bipolar depressions (3). Little research has been conducted concerning the application or blood levels of bupropion and clinical response. Preskorn (4) reported that trough levels in the range of 25–100 ng/ml produced maximal clinical response. Golden et al. (5) found that responders with a mean trough level of 21.7 ng/ml (SD=3.1) had lower trough levels than nonresponders (mean=41.2 ng/ml, SD=17.1); however, this result was not significant because of the small sample size. The peak bupropion blood level of any responder was approximately 30 ng/ml.

On the basis of these results, it was hypothesized that in a preliminary open study, patients who responded to bupropion would have trough blood levels in the range of 10–29 ng/ml and nonresponders, levels of 30 ng/ml or more.

## METHOD

Twenty-three patients who met *DSM-III-R* criteria for major depressive disorder were administered bupropion on an open basis. The patients consisted of seven men and 16 women with a mean age of 47.6 years (SD=14.3); there were eight bipolar and 15 unipolar depressed patients. All patients gave informed consent after the procedure was fully explained.

Bupropion treatment was initiated with a dose of 75 mg t.i.d.; the dose was increased by 75 mg every third day until response or a maximum dose of 450 mg/day was achieved. Trough blood levels were obtained 12 hours following the previous dose after at least 7–10 days of stabilization of the final dose; this occurred usually between 3 and 4 weeks after treatment was begun.

Patients returned for follow-up appointments after 2, 4, 6, and 8 weeks of treatment. At each visit, the Beck Depression Inventory was completed; patients were specifically queried regarding time to onset of improvement and presence of and change in side effects.

Statistical evaluation included one-way analysis of variance (ANOVA) with t tests to contrast responders (defined as patients who had at least a 50% decrease in Beck Depression Inventory scores) and nonresponders in terms of dose and trough blood levels and one-way ANOVA with t tests to contrast patients with blood levels of 10–29 ng/ml to others with blood levels of 30 ng/ml or more in terms of change in Beck Depression Inventory scores. Finally, time to onset of significant response was contrasted to time of onset and time of conclusion of side effects.

## RESULTS

Fifteen (65.2%) of 23 patients showed significant response to bupropion. The mean Beck Depression Inventory scores of responders improved from 24.7 (SD=8.2) to 6.1 (SD=4.3). Responders did not differ significantly from nonresponders in terms of mean age, diagnosis, bupropion dose, or baseline Beck Depression Inventory scores. Mean dose for responders was 423.3 mg/day (SD=77.6); mean dose for nonresponders was 450.0 mg/day (SD=0). Dose did not cor-

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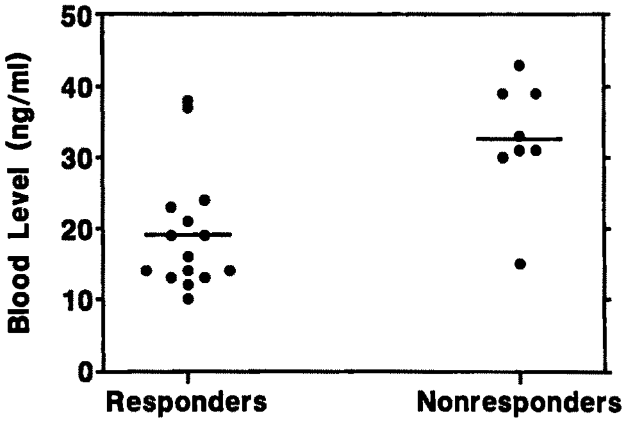
**FIGURE 1. Trough Blood Levels of Depressed Patients Who Responded (N=15) or Did Not Respond (N=8) to Bupropion**



relate significantly with blood level (r=0.26). However, responders did have a significantly lower trough blood level (mean=19.1 ng/ml, SD=8.6) than did nonresponders (mean=32.6 ng/ml, SD=8.6) (t=3.61, df=21, p=0.002). Figure 1 presents data on the bupropion blood levels of responders and nonresponders. The blood levels of responders were 10–38 ng/ml; the blood levels of nonresponders were 15–43 ng/ml. As would similarly be expected, patients with blood levels in the range of 10–29 ng/ml had significantly greater change in Beck Depression Inventory scores than those with blood levels of 30 ng/ml or more (mean=19.4, SD=6.8 versus mean=–0.8, SD=8.4; t=6.79, df=21, p<0.001) and proportionately more patients with a significant response (13 [92.9%] of 14 versus two [22.2%] of nine; $\chi^2$=12.05, df=1, p=0.0009). Mean response to bupropion was at 4.6 weeks (SD=2.6). Further information on rate of response, side effects, and long-term use of bupropion has been reported elsewhere (6).

## DISCUSSION

In this preliminary study, patients with trough levels of bupropion in the range of 10–29 ng/ml showed significantly greater response than those with levels of 30 ng/ml or more. This result may have been affected by the open design, since bupropion dose was continually increased by lack of response, to produce higher blood levels in nonresponders. Although this possibility certainly does exist, the fact that responders did not differ significantly from nonresponders in bupropion dose somewhat mitigates this argument.

Furthermore, these findings of improved response to trough levels in the range of 10–29 ng/mg certainly are consistent with the suggestion of Golden et al. (5). The relationship found by Golden et al. (5), that hydroxybupropion levels were better related to response than bupropion levels alone, could not be replicated in the present study because of lack of availability of these measures. Obviously, more double-blind studies with larger sample sizes are needed. It should also be noted that bupropion was well tolerated, with a 93% response in the suggested blood level range.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

MIND AND BRAIN

**The Remembered Present: A Biological Theory of Consciousness,** *by Gerald M. Edelman. New York, Basic Books, 1990, 336 pp., $32.95.*

A curious phenomenon: just when psychiatry has beaten a wholesale retreat from overarching theory to a not always finely targeted empiricism, neuroscience has swung in the converse direction—to admit the paraphernalia of cognitive science and artificial intelligence and even consciousness, that elusive but incendiary taboo construct. Consciousness used to be systematically cold-shouldered, but even quite respectable investigators now dedicate their efforts to discovering where it lurks and how it works. No one has done this more strenuously or with more perseverance than the author of *The Remembered Present.*

A convenient windmill to tilt at always makes a good start. Long dominant, hierarchical theories of brain organization have taken a beating of late. Parallel processing and reciprocal circuitry are in. Edelman joins the growing group of theorists who have realized that problems of cognition are not solved but only kicked upstairs by shuttling information to higher and yet higher centers. Instead, the neural network must have a repertoire of states that correspond to the set of experiences. How is this correspondence accomplished?

Edelman takes advantage of the well-known property of cerebral organization by which cortico-cortical connections are reciprocal (not unidirectional, aft-to-fore, as previously supposed). His analysis relies on such "reentrant" circuitry, and he demonstrates some neat tricks that it can play. Such simulation is, of course, the cognitive science approach, and had the simulations been more numerous and more profound one would have taken the theory more seriously. Edelman, however, goes it alone, stomping imaginary opponents in cognitive science, artificial intelligence, and functionalism on his way, although they are the most likely source of help that his ideas so desperately need.

*The Remembered Present* is a dense, intense text and exhibits a voracious and eclectic intellect, but its speculations so greatly outstrip their data base that little may be lost if one defers reading it, pending the next, expanded edition, which presumably will incorporate enough compatible fact to sustain the reader's interest in the ideas.

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**The Science of the Mind, 2nd ed.** *by Owen Flanagan. Cambridge, Mass., MIT Press, 1991, 424 pp., $27.50; $14.50 (paper).*

It is not an uncommon assumption among psychiatrists and psychologists that they can do quite nicely without philosophy thank you very much. Yet the paradox is that it is impossible not to take a philosophical stance of some kind, and psychiatrists and psychologists are effectively logical positivists or pragmatists and not very good ones at that.

Psychology and psychiatry are built on a complex network of usually unsuspected and unexamined metaphysical and epistemological assumptions. Different psychological schools start from different assumptions and, of course, reach different conclusions.

These schools then battle, sometimes for decades, as in the case of psychoanalysis and behaviorism, over their conclusions. Unless the combatants recognize and address their underlying assumptions, such battles are probably doomed to be fruitless, inconclusive, and unending. Add to this the fact that all too often proponents of one school have only a superficial knowledge and understanding of the proponents of the other schools and the prospects for the resolution of differences obviously become very bleak.

It would be extremely helpful to have a book that lays out the philosophical grounds and assumptions of different psychologies, and this is just what Owen Flanagan's book does. Flanagan carefully examines the claims of different schools of psychology and approaches to the mind, including those of Descartes, William James, Sigmund Freud, B.F. Skinner, Piaget, and Lawrence Kohlberg. He also examines cognitive psychology, artificial intelligence, sociobiology, and the nature of consciousness. He explores the underlying assumptions and logic as well as the validity and scope of each school's claims.

Flanagan has done his homework well. He has a deep knowledge of both psychology and philosophy, has carefully studied the different schools and their related research, acknowledges his own biases, and is scrupulously fair. I found only one very small dubious area, which involved a critique of Kohlberg's suggested seventh stage of moral development. Flanagan dismisses this as the product of "a weak mystical moment," but his dismissal appears to reflect a misunderstanding of mysticism, which, in addition to being the subject of much popular nonsense, has also been the focus of some of the world's greatest philosophers—Plato, Plotinus, Shankara, Chuang Tzu, and Ibn El-Arabi to name only as many as can be counted on one hand. This is a very minor fault in an otherwise excellent work. I know of no other that provides such careful and penetrating introductions to the philosophical assumptions and implications of major psychological theories.

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**Body Images: Development, Deviance, and Change,** *edited by Thomas F. Cash and Thomas Pruzinsky. New York, Guilford Press, 1990, 361 pp., $39.95.*

This very interesting book covers an important area to which psychiatry has not given adequate attention. The editors, together with 15 other contributors, have undertaken the subject of the psychological and social aspects of body images. In doing this, they tell us that they will answer the following questions: What are the meaningful components of the construct of body image and how are they best measured? What are the physical, developmental, social, and cultural determinants of body image? How do gender and objective attributes of appearance influence the subjective experience of the body? What are the roles of body images in development, change in personality, and psychopathology? How do deleterious changes and physical appearance and physical competence affect body images? How can one promote adaptive change in body image through the self-management of physical aesthetics, through medical-surgical procedures, and through psychotherapeutic and somatopsychic interventions?

The book starts with Seymour Fisher's learned outline of the history of the evolution of psychological concepts of the body. Fisher pays particular attention to the contributions of Paul Schilder and of psychoanalysis. The second part of the book, which I found its most interesting section, is devoted to the development of body images. Here Thomas Cash devotes a chapter to the psychology of physical appearance. The effects of stereotyping are described in the statement, "What is beautiful is good and what is ugly is bad." People do assume that those who are good-looking possess socially desirable personalities and are happier and smarter than those who are less attractive. Cash discusses the social and psychological consequences of this and other stereotyping; he notes that several studies have shown that more attractive men and women are favored over those who are equally qualified but less attractive in a variety of employment situations. There are many other social spinoffs of this phenomenon; for example, in the criminal justice system those who are less attractive tend to receive harsher treatment.

April Fallon discusses the changing concepts of beauty. She points out that women in our society are expected to be thinner today than before; for men the standard continues to be moderate mesomorphy. Beauty has been associated with wealth throughout history and in different cultures. Fallon points out that upper-class aristocratic women were once expected to be fat, then thin and delicate, and now firm and fit. She also notes that beauty practices of other cultures, such as scarification of the cheeks, changes in the skull and neck, and ornamentation of the mouth and lip, are considered deformations by Westerners. In the United States, she says, there has been a change in desirability of breast size: the introduction of silicone implants in 1962 led to the popularity of breast augmentation; however, by the late 1970s this demand had leveled off, and plastic surgeons reported that the trend in the East Coast was toward breast reduction.

Norman Bernstein, who is an expert on the care of patients who have been facially burned, contributes a chapter that contains several interesting case discussions providing insight into the patients' methods of coping with such disfigurement. Thomas Pruzinsky devotes a chapter to psychopathology of body images; he discusses hypochondria, body dysmorphic disorder, somatic delusions, gender identity disorders, depression, sexual dysfunction, and schizophrenia in terms of bodily experiences. The association between body image and eating disorders is well discussed by James Rosen. The book also deals with change in body image through reconstructive surgery and through psychological change. In the last section, the two editors present an integrative approach to the development, deviance, and change of body images.

This is a comprehensive undertaking in an area of importance and great interest to psychiatrists. The editors have selected authors who write well and who make important contributions that should be of interest to psychiatrists and others involved in behavioral sciences.

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## PERSONALITY AND ITS DISORDERS

**Cognitive Therapy of Personality Disorders,** *by Aaron T. Beck and Arthur Freeman. New York, Guilford Press, 1990, 396 pp., $35.00.*

Designed for the treatment of depression and extended to the treatment of anxiety disorders, cognitive therapy stakes a claim with this volume to treatment of the personality disorders (1, 2). Along with interpersonal therapy (3), cognitive therapy is one of the most popular therapies in clinical trials today, and the inclusion of another diagnostic domain under its purview is an event that merits notice.

The book is divided into two parts. In the first, the authors review the history, theory, and research bearing on cognitive therapy. In the second, they devote chapters to each of the types of character disorder. Cognitive theory holds that an individual's genetic proclivities interact with his or her family environment in the development of stable cognitive structures, or "schemas." The schemas guide the person's moment-to-moment thoughts, feelings, and interpretations in reaction to life, although the person is unaware of them. The schemas are learned, not developed as conflict-resolving structures, not repressed, and not actively resisting awareness.

As outlined in the first part of the book, cognitive therapy's techniques include "guided discovery" to recognize dysfunctional patterns of interpretation, "labeling of inaccurate inferences" to help the patient become aware of his or her automatic biases, "noting automatic thoughts" that potentially signify such biases, "collaborating" with the patient to test the validity of the patient's interpretations (e.g., how the patient tends to explain other people's behavior), "scaling extreme interpretations" (from 1 to 10) to counteract tendencies to all-or-none thinking, "reattribution" or reassigning responsibility according to the corrected view generated by these techniques, and "maintaining a diary" of tendentious misinterpretations and success in efforts to deal with them. Reference is frequently made to more detailed instruction available in earlier books, especially the original texts of Beck et al.

Although all of these techniques are generically useful, certain additional measures are of special importance in work with patients with character disorders. The authors use quotation marks around the word "transference" suggesting that it means something other than it does traditionally, but they use it to mean anger, disappointment, or frustration that grows out of distorted interpretations in the treatment relationship and can interfere with collaboration if not explored, which seems quite traditional. They also describe a technique called "reliving childhood experiences," which they note is not crucial in acute depression or anxiety but is emphasized for work with patients with character disorders. This technique involves a review of childhood experiences aimed at understanding the origins of nonadaptive patterns. In addition to simple recollection, role playing and reverse role playing of key interactions enhance this technique in changing core beliefs and reconceptualizing important figures of the past. The authors stress the particular importance of the therapist's scrutinizing his or her own automatic thoughts about patients during or outside of sessions. This is because patients with character disorders are often adroit in evoking feelings and behaviors that justify and confirm their own maladaptive reactions and schemas.

The second section of the book demonstrates the theory and techniques of cognitive therapy in relation to specific categories of character disorder. The authors describe the schemas that characterize each disorder and demonstrate with case vignettes and dialogue how particular techniques are applied. Schemas typical of avoidant personality disorder, for example, include, "I am socially inept and undesirable." "Others are potentially critical or rejecting." and "I cannot tolerate unpleasant feelings." Typical of obsessive-compulsive personality disorder are, "I am fully responsible . . . others tend to be too casual." "Any flaw may lead to catastrophe." "If I can't have systems, everything will fall apart." Those of antisocial personality disorder include, "People will get me if I don't get them first." "Cheating is okay as long as you don't get caught." and "What others think of me doesn't matter."

Cognitions subserving these organizing constructs are also illustrated. For example, typical of antisocial personality disorder are justification ("Wanting justifies action."), feelings make facts ("I'm right because I feel right about what I do."), and low-impact consequences ("What's undesirable won't occur or doesn't matter."). In a vignette on borderline personality disorder, the authors diagram the stages in impulse control: identify the impulse before action, inhibit automatic action, identify alternatives, select a response. Each stage is a place for possible and particular therapeutic intervention. For narcissistic personality disorder, the authors outline beliefs alternative to those typifying the disorder that can be tried on and reached for by the patient; for example, "Be ordinary. Ordinary things can be pleasurable." and "Others have needs and opinions that matter too." A diagram may also be helpful for the patient with obsessive-compulsive personality disorder. Recognition that the basic schema of this disorder ("No matter what I do, it won't be acceptable.") generates cognitions that cause avoidance and self-defeating meticulousness, which reaffirm the underlying sense of failure and unacceptability, can give the patient a cognitive handle for change.

The strengths of the book—and of the method—are several. The book lays down in elegant simplicity the fantasies that organize and guide people's behavior, and it links and labels fantasies that are typical and prominent in particular disorders of character. The book also names and defines the particular mental activities that impose dysfunctional ideas on a differing reality, such as dichotomous thinking, negative or personal attribution, catastrophyzing, and idiosyncratic meaning; thinking is believing. These are, in another parlance, the engines driving defenses. Labeling them can help therapists to recognize their enactment and thus to reflect them to patients, who can in turn recognize them and then grapple toward change. The book's illustrations show the slow, step-by-step, and delicate yet direct confrontation required to help patients grasp and alter their distorted thinking. Finally, the book provides an organized approach to active intervention and an overall treatment plan, sometimes including (without acknowledgment) the analysis of defense (for example, "Let's examine together what you just felt and thought in reaction to what I said.").

From another perspective, the book's and the method's attributes are also its limitations. Clarity and simplicity become oversimplification and naiveté in several instances. Suggestions that the therapist make a point of proving his or her trustworthiness to the patient with paranoid personality disorder because "it takes time to establish trust with most paranoid individuals" might bring a smile to therapists burned and spurned after having made such efforts. The idea that 50 weekly sessions could change a person with antisocial personality disorder seems similarly naive. (I thought that the patient described as having paranoid disorder was actually obsessive and dependent with paranoid features and that the patient described as having antisocial personality disorder—who showed a clear desire to please and be liked by the therapist—appeared not to have the pure form of this disorder.)

Perhaps the most costly virtue of the cognitive method is its base in learning theory. According to the book, for example, a bullied child becomes a bully by imitative learning. Such a view neglects the transmuting role and importance of emotions. No mention is made of the idea that the bullied child feels rage and helplessness and that he bullies later as an expression of chronic anger at those who are or were stronger and those whose weakness reminds him of his own. There is more to the development of such qualities, and all of character, than learning alone.

Despite these limits, the book is an excellent text, well worth a read. It can provide helpful tools to recognize and organize cognitive mechanisms, and it can both guide and permit activity for the therapist schooled in psychoanalytic or other therapies. It is also a major contribution to the growing literature on cognitive therapy. To an old analyst, though, it is of interest to see that this volume stresses transference and explorations of the past, re-introduces countertransference, and notes that treatment of patients with character disorders can require more frequent than weekly visits and may endure for up to two and a half years. That the founder of cognitive therapy, after 15 years of experience, can come to such concordance with the psychodynamic therapy this treatment aimed to replace makes one rather wonder.

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**Toward a New Personology: An Evolutionary Model,** *by Theodore Millon, Ph.D. New York, John Wiley & Sons, 1990, 177 pp., $29.95.*

Theodore Millon's latest book rides the shifting tides of psychology and psychiatry toward renewed interest in the study of personality and its disorders. After a period in the 1960s and 1970s when personality concepts such as disposition, stability, and generality came under attack by what Millon terms the "anticoherency and anticonsistency movements," the time is once again ripe to develop theories of personality to guide inquiry into the foundations of personality attributes and to unify the classification, assessment, and treatment of personality disturbances. Revival of interest in "personology" has been stimulated by the increased emphasis by mental health practitioners on outpatient care, the enhanced status given to personality disorders in the *DSM-III* multiaxial system, and the births of an international society, a congress, and a journal devoted to the study of personality disorders.

Millon's approach is to borrow principles and substance from more established, advanced sciences in order to escape the "horizontal refinements" in personality theory that he believes have characterized developments over the past 40 to 50 years. The sciences from which his inspirations and content spring are physics and evolutionary biology.

Of this short book (it can be read, although undoubtedly not fully appreciated, in just a few hours), Millon devotes roughly half to the explication of his theory. He begins by describing analogies between evolution and ecology on the one hand and personality on the other. The so-called complex adaptations and strategies of organisms seeking to survive and to reproduce (two essential components of fitness according to Darwin) are likened to personality styles and structures. Millon describes the four domains or spheres in which evolutionary and ecological principles are demonstrated: existence, adaptation, replication, and abstraction. From the first three, he describes "polarities" of process creation versus destruction, accommodation versus modification, and propagation versus nurturance, respectively. From these he derives three corresponding "personality polarities"—pleasure versus pain, passive versus active, and self orientation versus other orientation—which become the fundamental distinctions in personality structure and function. The material might be somewhat heavy going for the readers who, like me, have most of their basic science knowledge (who can state the difference between the r-strategy and the K-strategy of reproductive behavior?) packed in the basement trunk with lab coats and dissecting kit. To Millon's credit, however, the explication is clear and understandable.

The reader is presented next with the personality theories of Freud, Eysenck, Gray, Buss, Russell, Tellegen, Cloninger, and others, whose tripartite models theoretically align strikingly with Millon's evolution-derived polarities. The concepts of pleasure versus pain, passive versus active, and self versus others are demonstrated to be often-occurring themes in the diverse psychological domains of learned behaviors, unconscious processes, emotion, motivation, and their biological substrates.

Following the theoretical argument is a discussion of the *DSM-III-R* personality disorders from the perspective of personality polarities. Personality disorders, according to Millon, result from deficiencies or imbalances in or conflicts between aspects of one or more of the polarities. In Millon's construct of personality disorders, there are 10 basic types and three severe, dysfunctional types (schizotypal, borderline, and paranoid). As an example, narcissistic personality disorder is characterized by primary reliance on self and passive adaptation.

After nosology, Millon describes his own three self-assessment measures. The Millon Personality Type Questionnaire assesses the balance and pattern of a person's three evolutionary polarities. The Millon Personality Disorder Checklist (described in greatest detail) examines eight domains of personality structure (e.g., self-image, mood/temperament) and function (e.g., interpersonal conduct, regulatory mechanisms) that enter into the clinical assessment of personality. Finally, the Millon Clinical Multiaxial Inventory yields a profile of personality disorders per se.

In the final section of the book, Millon discusses the need for integrative therapy for personality disorders. "Integrative" is distinguished from "eclectic" in that the latter involves wise selection from among separate techniques, whereas the former consists of designed composites and progressions among diverse techniques, based on the specific psychological structures and functions causing the patient's problems. This last section is the least well-developed of the book, presumably awaiting a more comprehensive treatment in the future.

On page 14 of *Toward a New Personology,* Millon states that theories "provide the basis for generating hypotheses and stimulating new knowledge." In the book's epilogue, Paul Meehl is quoted as saying, "To 'justify' concocting a theory, all one needs is a problem, plus a notion . . . of how one might test one's theory." It seems fair to ask how this new theory of personology does in generating testable hypotheses. A number of the problems confronting those attempting to make sense of the classification of personality disorders today echo through the pages of the book.

First, personality is proposed as coherent and consistent. The types of personality disorders described by Millon are theoretically distinctive on the three polarities, but can this be shown empirically? Co-occurrence of personality disorders is common in clinical settings, and Millon describes overlap between severe types and basic types, but what of the observed "comorbidity" between narcissistic and antisocial or avoidant and dependent disorders, pairs differing on the passive-active polarity, in which poles are presumed to be mutually exclusive? Axis I and axis II disorders are said to be related to polarities. What distinguishes the two axes or, for example, social phobia from avoidant personality disorder?

Second, certain aspects of personality, it is argued, are stable over time and pervasive in many situations and contexts. Can polarities or derived clinical domains be demonstrated to have greater stability and pervasiveness than traits otherwise defined?

Third, there is an assumption that normal and abnormal personalities are a matter of degree. Are polarities or domains or their combinations found continuously distributed in the general population? Are any types restricted to patients or to individuals with recognized disability?

Finally, can polarities or domains be shown to have value in understanding pathogenesis or in guiding treatment and predicting outcome?

Millon speculates that some readers will find his conjectures "persuasive, a few more will consider them 'interesting' . . . still others will find little merit in them." I guess I place myself in the "interested" group—stimulated, but waiting to be persuaded.

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**Family Environment and Borderline Personality Disorder,** *edited by Paul S. Links, M.D., M.Sc., F.R.C.P.(C.). Washington, D.C., American Psychiatric Press, 1990, 159 pp., $22.50.*

In the final chapter of this slim but provocative book John Gunderson summarizes the conclusions of the eight chapters by underscoring the centrality of heterogeneity in the pathogenesis of borderline personality disorder. Although this might not seem a landmark finding for those of us who have muddled through the conceptual scaffolding of the borderline concept, Links's focus on the research aspects of the impact of the family environment on borderline pathology does provide a fresh look at the data.

In the first chapter, Links and Heather Munroe Blum state that "all formulations of the etiology of borderline personality disorder have stressed the importance of the family environment." This conclusion is presented against the backdrop of *DSM-III-R,* which they say provides no information on the predisposing factors and familial pattern of borderline personality disorder. Links and his colleagues attempt to fill in the blanks from the perspective of family influences.

Even a casual reading of the literature on borderline personality disorder underscores the influences of both parents and of the family on the pathogenesis of this disorder, although it is not always clear whether some of their influences (which include failure of both parents, sexual abuse, and impulsivity) determine the onset or the course of the disorder. However, some of the conclusions in this book are not always in keeping with our clinical attitudes toward borderline personality disorder. For example, some of the dynamic hypotheses relating traumatic separations and losses to the cause and onset of borderline personality disorder are not borne out by the research. Clearly, there are specific familial influences, but causal relationships and hypotheses concerning borderline personality disorder are not always demonstrated when large numbers of borderline patients are studied.

Evidence is also provided that borderline personality disorder is a valid psychiatric disorder. In one study it was revealed that family members of patients diagnosed as having borderline personality disorder had a greater prevalence of borderline personality disorder in their first-degree relatives. Moreover, alcohol and affective disorders among first-degree relatives also pointed to familial linkages. Another finding provides a different understanding of the gender differences in borderline personality disorder: more women than men are diagnosed as borderline, and one of every nine women with borderline personality disorder has been sexually abused. It is now argued that these gender differences, rather than pointing to a specific etiologic pathway for borderline personality disorder, may suggest a different diagnosis, namely, posttraumatic stress disorder. Alternatively, the trauma of sexual abuse may serve as a marker rather than as a causative agent for borderline personality disorder.

In his summary chapter, Gunderson concludes that a linkage between borderline personality disorder and impulsivity may point to the possibility that dopaminergic or serotonergic systems are involved, suggesting potential areas for further research into the biogenic hypothesis of borderline personality disorder. However, in downplaying the effect of trauma on borderline personality disorder and supporting the view that it is the absence of stable structures, "soothing presences," and "active nurture or able substitutes" which may determine the development of borderline personality disorder, he is essentially taking a therapeutic position (a self psychology one) and arguing against a purely biogenic position. In keeping with the mission of this fine volume, Gunderson points to future research directions for those of us still bold enough to be fascinated by this clinical phenomenon.

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## FORENSIC PSYCHIATRY

**Principles and Practice of Forensic Psychiatry,** *edited by Robert Bluglass, M.D., F.R.C.Psych., D.P.M., and Paul Bowden, M.Phil., M.R.C.P., F.R.C.Psych. New York, Churchill Livingstone, 1990, 1,405 pp., $306.00.*

Forensic psychiatry is that challenging subspecialty arising from the intense overlap of two divergent systems—psychiatry and the law. For many psychiatrists and other mental health clinicians, responding to the legal system is fraught with anxiety and misgivings. Indeed, the practice of forensic psychiatry requires special knowledge. Information regarding legal issues, critical assessment of psychiatric data, and the ability to communicate clearly are necessary. This comprehensive book helps provide much of the requisite knowledge to work in this robust area.

*Principles and Practice of Forensic Psychiatry* is a thoughtful, practical, and scholarly compendium of subjects related to forensic psychiatry considered from multiple perspectives. Nearly 150 contributors authoritatively discuss the British legal system, its historical basis, civil law, legislation, juvenile law, competency, criminal responsibility, clinical care, and community psychiatry. The book is outstanding in its practical guidelines. Its documentation of the relationship between specific mental disorders and criminal behavior is noteworthy. There is an excellent blending of current scientific information with practical clinical applications.

Most of the book centers on the United Kingdom, but some discussions are relevant to the practice of forensic psychiatry in other countries. The psychiatrist in the United States will find a detailed state-of-the-art review of forensic and clinical issues such as violence, personality disorders, deviant sexual behavior, and substance abuse. Unfortunately, relatively few landmark cases from the United States receive attention. For instance, only 14 of the approximately 50 legal cases on the reading list of the American Board of Forensic Psychiatry are covered. However, the information on the early tests of insanity, on historical figures, and on legal concepts is useful.

In areas where I consider myself to be reasonably informed, the topics are adequately covered and the discussion valuable. In areas where my knowledge is more limited, I found the book informative and enlightening. In short, *Principles and Practice of Forensic Psychiatry* is an excellent, practical, up-to-date resource for professionals willing to brave the hazards of the legal arena.

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**A Conflict of Rights: The Supreme Court and Affirmative Action,** *by Melvin I. Urofsky. New York, Charles Scribner's Sons, 1991, 261 pp., $22.95.*

Affirmative Action and the social and economic conditions that gave rise to it as a public policy are very complex areas. In *A Conflict of Rights,* Melvin Urofsky, a professor of both history and Constitutional law, presents a clearly written story of the complex case of *Johnson v. Transportation Agency,* a case that reached the Supreme Court and involved difficult questions of both law and social policy. In 1974, Diane Joyce and Paul Johnson both applied for the position of road dispatcher, a job in the skilled craft category, in the Santa Clara County Transportation Agency. Diane Joyce had worked for the county since 1970, serving as an account clerk until 1975. In 1974, she applied for the road dispatcher position but was ineligible because she had not served as a road maintenance worker, a prerequisite for the job. In 1975, she transferred from a senior account clerk position to a road maintenance position, becoming the first woman to fill that job. During her 4 years in that position, she occasionally worked at the job she coveted, that of road dispatcher.

Paul Johnson began work for the county in 1967 as a road yard clerk. He, too, applied for the road dispatcher position in 1974 and was turned down. In 1977, he began work as a road maintenance worker and during the next 2 years occasionally worked as a road dispatcher.

In 1979, Joyce and Johnson competed for the job of road dispatcher. Paul was certain that he had the job, having been told by people who should know that he would get it. Joyce feared that she would be kept out of the job by an active "old boy" network. She appealed to the County Affirmative Action officer and ultimately, with that officer's intercession, was awarded the job as part of the county's Affirmative Action program. Paul Johnson thought he deserved the position (and he had been told he would get it) and that reverse discrimination had occurred. Therefore, he began a struggle over the right to be hired that went from the Santa Clara County Court to a Court of Appeals to the Supreme Court of the United State.

In an opinion issued on March 25, 1987, Justice Brennan, writing for the majority, affirmed Diane Joyce's right to a job granted to her by virtue of Affirmative Action. Brennan wrote, "We therefore hold that the agency appropriately took into account . . . the sex of Diane Joyce in determining that she should be promoted to the road dispatcher position. The decision to do so was made pursuant to an Affirmative Action Plan that represents a moderate, flexible, case-by-case approach to effecting a gradual improvement in the representation of minorities and women in an agency's work force. Such a plan is fully consistent with Title VII for it embodies the contribution that *voluntary* employer action can make in eliminating the vestiges of discrimination in the work place. Accordingly, the Judgment of Appeals is affirmed."

*A Conflict of Rights,* the absorbing story of this case, tells the story of two hard-working county employees who both believed that they were right in their pursuit of a job. It tells the story of the lawyers and the courts that supported them in their struggle for justice. A reader gains insight into the workings and machinations of the legal system and the personalities of the individuals involved, including but not limited to the members of the 1987 Supreme Court that issued the decision. Finally, a very detailed description of the history of litigation surrounding Affirmative Action is chronicled through a review, inspection, and interpretation of the case adjudicated by the Supreme Court. *A Conflict of Rights* probably will not share a place with other great books written about Supreme Court justices and the inner workings of the Supreme Court (as in *The Brethren* [1]) or about landmark cases such as *Brown v. Board of Education, Gideon v. Wanewright* (*Gideon's Trumpet* [2]), or *Rowe v. Wade.* On the other hand, it presents an interesting story, a human story, and an illustration of the ongoing struggle of the Supreme Court to define the boundaries of Affirmative Action, a remedy for past racial, religious, or sexual discrimination.

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## SUBSTANCE ABUSE

**Alcohol and the Family: Research and Clinical Perspectives,** *edited by R. Lorraine Collins, Kenneth E. Leonard, and John S. Searles. New York, Guilford Press, 1990, 386 pp., $40.00.*

There are a lot of books available on alcohol abuse, but few of them are very good. This book is one of the best I have seen for a while. It is an interesting combination of research and clinical material. The complex relationship between alcohol abuse and the family is an area worthy of more investigation, and the authors make important contributions to the understanding of this issue. The book is divided into three sections: Genetic Research, Family Processes, and Family Treatment. All of the chapters are clear and contain new information as well as clinical material.

The chapter critiquing genetic studies differs from other summaries by giving more detail on research methods. It also compares different ways of studying the family. The material it provides on twin studies is detailed and well explained. The problems of genetic studies range from statistical appropriateness to basic concepts. This chapter is well referenced, and the bibliography could serve as a guide for people looking for further reading.

The next chapter focuses on the implications of current research for our understanding of alcoholism as a familial disease. There is a good overview of adoption studies. The interaction between genes and environment is discussed, as are concepts of the disease model. The comorbidity of alcohol abuse and personality disorders is well presented and scientifically evaluated. This chapter is particularly well documented and has copious references.

The discussion of genetics and alcoholism continues in chapter three with the search for biological markers for the vulnerability to alcoholism and a discussion of the differences between state and trait markers for alcoholism. It also reviews the metabolism of alcohol and describes several markers under investigation. The next chapter deals with the general concepts of behavioral genetics and discusses models that best fit alcohol abuse. As with the preceding chapters, genetic transmission and distribution are well explained.

The second part of the book, Family Processes, begins with a discussion of the impact of the family on the patterns of adolescent drinking. This is put in the context of general problem behaviors, but the implications for the social effects on adolescent alcoholism are clear. This first chapter is good but seems too brief, given all the material it needs to cover.

Johnson and Rolf contribute an excellent review of the research concerning the children of alcoholics, covering topics ranging from fetal alcohol syndrome to the behavioral assessment of high-risk children. Citations are given to a large collection of fine articles regarding the family, culture, and transmission of alcoholism.

An excellent chapter by Leonard reviews the marital interactions of different kinds of alcoholics, providing a very interesting comparison of episodic and steady drinkers. Unfortunately, the list of references is a bit short, a drawback to the researcher interested in further reading.

I was surprised to find an entire chapter devoted to the sexual functioning of male alcoholics. This important area seems to be uniformly overlooked in most texts on alcoholism. The physiological and psychosocial factors are discussed, the course and treatment of dysfunction are briefly summarized, and longitudinal studies are examined. This chapter could have been improved by adding more information about the sexual functioning of female alcoholics.

In the third section, there is a good chapter on the stresses of families dealing with alcoholic members. It describes the areas of family adaptation, communication, and problem solving. Much of this information is from original research and is quite interesting. The last part of this chapter deals with the effect of alcohol abuse on marital relationships. It includes information about gender differences, stress, and coping skills. Implications for treatment are objectively discussed for each area of pathological behavior.

This book has taken on a complex task: the examination of alcohol abuse and the family. It does a fairly good job of handling this material. The contributions by clinicians and researchers are interesting and make this book well worth reading.

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**The Nature of Drug Dependence,** *edited by J. Griffith Edwards and Malcolm H. Lader. New York, Oxford University Press, 1990, 233 pp., $59.95.*

*The Nature of Drug Dependence* is a nine-chapter volume from the Society for the Study of Addiction's semiannual meeting of the same title. This society publishes the well-respected monthly *British Journal of Addiction.* The focus of this special-invitation meeting was to bring together world experts in many disciples who work on the issue of drug dependence. Chapters were compiled from papers prepared for the meeting. Each participant received the papers before the meeting. Discussion was held after each paper and is included in an edited format.

Topics covered in this volume include historical concepts of dependence, genetic aspects of alcohol and substance abuse, and the cellular biology of tolerance and dependence. Two chapters focus on drug-seeking behavior. All chapters are well-written by internationally recognized experts.

The final chapter serves as a synthesis in the study of dependence. Written by Jim Orford, this chapter reviews the complexity of studying and understanding drug dependence. He states, "We have to face up to the fact that dependence—itself a multidimensional concept—has many and varied determinants in the biological, psychological, and sociocultural domains, and that these variables interact in complex ways." He goes on to suggest that there are no simple prevention or research solutions. Prevention might best be served by a multifaceted approach targeting early behaviors as well as later behaviors. Research advances are likely to rely on multidisciplinary teams.

The final chapter's discussion highlights the problems of multidisciplinary research. There is a paucity of knowledge and research regarding the nature of multidisciplinary collaboration. University departments often discourage collaboration by dissertation and tenure requirements. Despite these and other problems, the participants cite examples of successful multidisciplinary teams.

This volume's attraction is the combination of excellent and well-referenced chapters with discussions by world leaders in the fields of alcohol and drug dependence. Because of the wide scope of the topics selected, readers are likely to find some chapters less informative than others. As a whole, however, this collection is important for researchers in the area of drug dependence. Some clinicians specializing in alcohol and drug dependence might also find it worthwhile.

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**Alcohol and Seizures: Basic Mechanisms and Clinical Concepts,** *edited by Roger J. Porter, Richard H. Mattson, Joyce A. Cramer, and Ivan Diamond. Philadelphia, F.A. Davis, 1990, 342 pp., $65.00.*

This volume addresses the interaction between alcohol abuse and seizure disorders. The editors focus on the neurological and basic science bases of these two important clinical entities as well as their clinical and therapeutic interactions.

The interaction between alcohol and seizures is clearly an emerging field at both the basic science and clinical levels. From a clinician's standpoint, this book would have been more readable if the section entitled Classification and Diagnoses of Syndromes had preceded Basic Mechanisms of Alcohol-Related Seizures. As it is, the reader is asked to dive into the cell biology and physiology of alcohol as well as its mechanisms and its effects on the nervous system after only a brief introduction. I found that rereading this section after I had been grounded in the latest thinking relative to the classification and diagnoses of the interaction put this basic science material into a more cogent context.

This work, however, is important reading for psychiatric clinicians. It is especially important for those who work in the substance abuse area. For example, it includes the latest research and thinking relative to the alcohol withdrawal syndrome. This syndrome is examined in terms of its neural excitability, molecular pathways, drinking patterns, and clinical descriptors. Treatment modalities are also described in terms of this period of heightened excitability. The alcohol withdrawal syndrome is compared with other seizure patterns, especially in individuals who have seizure manifestations from other underlying causes.

The editors have endeavored to provide a diverse and rich mix of sophisticated views in this dual-diagnosis area. Although we know a number of facts about the alcohol withdrawal syndrome and its seizure component, there is much that is still unknown and unanswered. This book ends with a description of these unanswered issues in counterpoint with the known issues and treatment approaches.

This work is a sophisticated volume in an emerging field. It is written primarily by neurologists and basic scientists, but it has a great deal of relevance to clinical psychiatrists, especially those involved in addictionology.

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**Treatment Choices for Alcoholism and Substance Abuse,** *edited by Harvey B. Milkman, Ph.D., and Lloyd I. Sederer, M.D. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1990, 379 pp., $49.00.*

Alcoholism and drug addiction are matters of major concern both in Western and Eastern countries. This book answers the need to circulate updated information on these topics among the entire scientific community—not just medical personnel—to promote an interdisciplinary approach and avoid an "unidimensional reductionism and simplistic explanation in a field beset by complexity."

The first section of this book, Biological Factors, reviews the genetic influences (Allan Collins and Christopher de Fiebre), the biochemistry of mood and behavior (Stanley Sunderwirth), the biological approach to addiction treatment (John Renner), and nutrition and recovery (Lee Ann Mjelde Mossey). These papers make available updated information on different types of addiction and underlying biological mechanisms. In particular, Sunderwirth mentions the evidence indicating that it is possible to modify the chemistry of the brain by diet and exercise. He also postulates the occurrence of a natural high by such acts as hang gliding: "As the pilot approaches the edge of the cliff and then soars into space, there is a rush of excitatory neurotransmitters into the synapse, which brings about an immediate increase in the rate of neuronal firing . . . and in turn results in a elation of mood, and increased alertness, and a complete elimination of either drowsiness or depression." This seems to be an expensive and risky way to treat depression underlying addictive behavior.

In the second section of the book, Prevention and Recovery From Alcoholism, Peter Nathan shows that it is easier to prevent some consequences of alcohol misuse than it is to prevent chronic abuse itself. Other chapters include "The Assessment and Treatment of Alcohol- and Drug-Related Traffic Offenders" by David Timken, "Prevention and Intervention in Schools" by Mary VanderWall, and "Employee Assistance Programs as an Early Intervention Strategy for Substance Abuse" by Carol Hacker.

Timken points out that alcohol abusers are likely to become traffic offenders; he found that recidivism was consistently higher among offenders who failed to complete the educational program in the Colorado judicial system. Hacker's paper stresses that substance abuse is a major concern for companies. The National Institute on Drug Abuse reports that 23% of all workers use drugs on the job and that 5% have substantial addiction problems.

Part three of this book, Multiproblem Patients, contains contributions by Lloyd Sederer ("Mental Disorders and Substance Abuse"), Sheila Blume ("Alcohol and Drug Problems in Women: Old Attitudes, New Knowledge"), and George Vaillant ("Elements of Recovery: A Longitudinal Analysis").

Part four, Treatment and the Law, contains, among others, papers by Alexander Hunter and Robert Pudim ("Treatment Strategies for Juvenile Delinquents to Decrease Substance Abuse and Prevent Adult Drug and Alcohol Dependence") and Phillip Sidoff et al. ("Rehabilitation of Multiple DUI Offenders: An Innovative Model"). All of these contributions point out that in the management of alcoholism and drug addiction knowledge of forensic psychiatry is at least as important as knowledge of clinical psychopathology and psychopharmacology.

Finally, in part five, Treatment Alternatives, William Miller discusses "Alcohol Treatment Alternatives: What Works?" He points out that there is no overall advantage for residential, intensive, or longer treatment over less expensive alternatives. In "Cognitive-Behavioral Treatment of Problem Drinking" Chad Emrick and Gregory Aarons deal with established behavioral procedures. Other chapters in this section include "Affective Modes in Multimodality Addiction Treatment" by Robert Vaughn Frye, "Family Therapy Approaches to Substance Abuse With a Special Focus on Alcohol Issues" by Victor Harris, "Therapy With Families of Adolescent Substance Abusers" by M. Duncan Stanton and Judith Landau-Stanton, and "Interventions With the Substance-Abusing Nurse" by Vernice Griffin Hills.

This book generally emphasizes social and educational factors that can promote or reduce the use of intoxicants rather than biological determinants and psychopharmacological management. It also mentions the intriguing concept of natural highs. The "natural" altering of our consciousness, providing increased pleasure, seems hardly applicable (and in some way misleading) in such situations as unhappiness, anxiety, or depression, which often underline alcoholism and drug addiction. Such conditions, which are at least partly biologically determined, cannot be affected simply by exercise or diet. They need proper diagnostic recognition and psychopharmacological and/or psychotherapeutic management. Moreover, this books does not include contributions on such recent biological findings as changes in cerebral blood flow and neuroimaging in drug addiction, molecular biology of alcoholism, and new treatment strategies of withdrawal syndromes.

In conclusion, this book could be of some interest to psychiatrists and to nonmedical staff for its prominent educational and social content; its main quality is in supporting (at least in principle) a multimodal therapeutic approach.

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**Cocaine in the Brain,** *edited by Nora D. Volkow, M.D., and Alan C. Swann, M.D. New Brunswick, N.J., Rutgers University Press, 1990, 188 pp., $40.00.*

This is a compact and friendly introduction to the neurobiological and phenomenological dimensions of cocaine abuse. The scope of the book, which is largely exclusive of treatment issues, neatly covers relevant topics. All chapters have been authored by well-known experts in cocaine research.

The text comprises eight chapters. The first, by Burt Angrist, is a tight comparison summary of cocaine and amphetamine that includes interesting speculation on the phenomenology of these drug-induced psychoses. The next chapter, about populations at risk for cocaine use, provides a useful summary of the epidemiologic data collected for the 1985 National Survey on Drug Abuse by the National Institute on Drug Abuse but may leave the reader with curiosity about more recent trends and for predictions of future at-risk groups. Roy Wise, writing on the neural mechanisms of the reinforcing action of cocaine, punctuates his summary of a highly complex literature with an excellent set of references. In a brief but stimulating section he speculates about the role of memory in cocaine craving.

Several chapters are devoted to the putative mechanisms of cocaine effects. The chapter by Alan Swann attempts to digest an extremely large body of preclinical data on acute and chronic effects of cocaine, covering behavioral effects, in vitro models, sensitization, kindling, and transmitter interactions. Despite the complexity of the topic, this chapter is highly readable. The author's necessarily cursory exploration of models and evidence is certainly sufficient to provide the reader with an appreciation of the intricacy of brain processes during and after cocaine use.

Nora Volkow follows with a chapter on the applications of imaging modalities. The sections on single photon emission computed tomography (SPECT), magnetic resonance imaging, computerized EEG, and CT seem to focus on descriptions of these technologies and are a bit short on practical application to studies of cocaine use in humans. Indeed, the use of iodinated dopamine receptor radioligands in SPECT has greatly expanded since the publication of this book, thus dating parts of it. The section on positron emission tomography is more developed and clinically meaningful; this is consistent with the more advanced state of research and the author's research interest.

The next chapter, by Charles Ashley and Robert Hitzemann, is a fine synopsis of the clinical pharmacology of cocaine, with clear figures and concise prose. This is followed by descriptions by Charles Dackis and Mark Gold of clinical aspects of cocaine use, including an inventory of medical sequelae of use, neuroendocrine alterations in cocaine withdrawal states, and the pharmacological management of cocaine abstinence. This chapter is a bit syncopated and moves suddenly from one topic to the next. In the final chapter, Frank Gawin and Everett Ellinwood present an overview of the clinical phenomenology of cocaine abuse. They refer to amphetamine effects and are generally careful to acknowledge differences between the two stimulants. One wishes more recent descriptive data were incorporated; there are no clinical references past 1986.

In all, the chapters clearly present the conventional wisdom that has been presented recently in more dense form as journal articles. (The epidemiologic and descriptive chapters might have benefited from survey of more current literature, however.) The chapter bibliographies are quite extensive and provide a very good reference base for those who wish to explore subjects in greater depth. These qualities, as well as the conciseness of the book, lead us to recommend it as a solid introductory text for medically or biologically trained students and professionals.

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*Reprints of Book Forum reviews are not available.*

# *Letters to the Editor*

## Blood Groups in Panic Disorder

Sir: Substantial evidence suggests that panic disorder runs in families, but the genetic locus, if any, has been elusive (1). One approach is to study chromosomal markers such as ABO blood type or human leukocyte antigen (HLA) in individuals with the illness. In early studies (2–4) investigators found a higher frequency of blood group O among patients with manic-depressive illness than among control subjects and a higher frequency of blood group A among unipolar patients. The finding of a relationship of panic disorder with certain blood groups would be a significant step toward understanding the disorder.

We incidentally observed that six of eight consecutively admitted patients with panic disorder had type B blood. This finding prompted further inquiry, and data were collected from 45 patients diagnosed as having panic disorder. Of these 45 patients, 14 patients had blood type A, seven had type B, one had type AB, and 23 had type O. This distribution of blood types was normal compared to that of the general population.

The search for a genetic marker for panic disorder has been disappointing, and our investigation suggests that blood type in panic disorder offers no new leads. However, the discovery of new probes continually raises hopes that a definite genetic marker for panic disorder and other important psychiatric disorders may be found soon.

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## An Unusual Presentation of Multiple Sclerosis

Sir: Behavioral changes, including alterations in cognitive functions and psychiatric abnormalities, have been recognized with increasing frequency in patients with multiple sclerosis (1, 2). Except for a single case report (3), the literature indicates that multiple sclerosis is usually diagnosed long before the appearance of any cognitive dysfunction (2, 4). We report an unusual case in which a frontal syndrome was the first manifestation of multiple sclerosis.

Ms. A, a 37-year-old woman, was referred to a psychiatric outpatient clinic by Social Services because of marital difficulties. A college graduate and mother of three young children, she was showing behavioral changes that had started insidiously 6–8 months prior to referral. When questioned, her family reported that she had no history of neurological or psychiatric disturbance. She was neglecting her household chores, engaging less in activities outside the home, and showing indifference toward her husband's complaints. Because of her apathy about her condition, she had not sought medical assistance but was brought to Social Services for counseling at her husband's insistence. The psychiatric liaison to Social Services examined her and found her fully oriented in time and place. Her affect was blunted, remote, and somewhat apathetic, and her thought processes were mildly slowed, with an impaired capacity for abstract thinking. Her vocabulary was surprisingly poor for a college graduate. She was unable to copy simple geometric forms or draw a clock. She demonstrated little insight with regard to her condition.

The abnormal cognitive functioning prompted a full neurological examination and workup, which disclosed bilateral frontal release signs, mild left-side pyramidal signs, and bilateral vibration loss in her legs. Laboratory studies revealed oligoclonal bands in her CSF. Visual evoked potentials were abnormal. Brain magnetic resonance imaging (MRI) showed generalized atrophy, with foci of long relaxation time in the white matter of the brainstem and cerebellum. Results of blood cortisol and thyroid tests and levels of vitamin $B_1$, vitamin $B_{12}$, arylsulfatase, hexosaminidase, and very-long-chain fatty acids were all normal. HTLV-I, HIV, and VDRL test results were negative.

Neuropsychological testing demonstrated a severe frontal lobe dysfunction, with difficulties in abstraction, concept formation, judgment, and praxis. In addition, there was marked mental slowing and mild attention deficit.

Ms. A fulfilled Poser's diagnostic criteria for "laboratory supported definite MS," having frontal, pyramidal, and posterior column signs, pathological visual evoked potentials, oligoclonal bands in the CSF, and a brain MRI compatible with focal demyelination. Her presentation was that of frontal syndrome, with organic personality disorder supported by neuropsychological testing.

The range of cognitive deficits in MS is broad (5). It appears that certain functions, such as conceptual processes and attention, tend to be preferentially impaired (4), as was true in this case. Organic personality disorder usually develops years after the diagnosis of multiple sclerosis (2, 4). Our case seems to be unique, because an overt organic personality disorder appeared to be the first manifestation of multiple sclerosis. We are reporting this case in order to stress the importance of careful neurological examination and extensive laboratory workup for young patients presenting with behavioral changes.

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## Cyproterone Acetate in the Treatment of Aggression

SIR: Medroxyprogesterone acetate has been reported to reduce aggression in patients with temporal lobe epilepsy (1) and in male schizophrenic patients (2). Its efficacy is thought to be due to its lowering of testosterone levels and competitive inhibition of androgen action in the brain. However, medroxyprogesterone acetate has major side effects, such as weight gain, feminization, and even adrenal insufficiency. We report here the efficacy of a new competitive inhibitor of androgen binding, cyproterone acetate, in three neuroleptic-refractory aggressive male patients. Cyproterone acetate is considered to be devoid of the side effects we have mentioned. All three patients consented to the trial.

> Mr. A, a 29-year-old man with mild mental retardation and intermittent explosive disorder, had a long history of unpredictable assaults. He was admitted to the hospital because he attempted to set a fire. During this hospitalization aggressive episodes, including verbal and physical assaults on staff members, occurred almost every day despite increasing doses of neuroleptic medication. His mean level of aggression was 19 on the Overt Aggression Scale (3). Cyproterone acetate was gradually added to the existing medications (sultopride, 2400 mg/day; levomepromazine, 400 mg/day; clorazepate, 150 mg/day), and Mr. A's aggressive behavior disappeared within 3–4 weeks. The maintenance dose of cyproterone acetate was 200 mg/day. This improvement has been maintained for 22 months and has permitted the patient to be discharged from the hospital. At this writing, the concurrent neuroleptic medication has been gradually reduced by more than 50% of the initial dose.
>
> Mr. B, a 30-year-old man with a diagnosis of infantile psychosis, had shown aggressive and impulsive behavior since the age of 10. During the months that he was on our ward, his level of verbal and physical aggression had gradually increased and reached 18 on the Overt Aggression Scale in spite of large doses of medications, including levomepromazine, 300 mg/day; carbamazepine, 600 mg/day; and diazepam, 200 mg/day. Following the administration of cyproterone acetate, increased to a dose of 200 mg/day, the patient showed clear improvement within 1 month. His aggressive behavior disappeared. The other medications were gradually reduced until Mr. B was taking only levomepromazine, 150 mg/day. After 4 months, when cyproterone acetate was discontinued for a month, the patient relapsed within 2 weeks, but his condition improved upon resumption of cyproterone acetate, 200 mg/day.
>
> Mr. C, a 40-year-old man with a diagnosis of disorganized schizophrenia, had a long history of psychosis with unpredictable assaults. He had been hospitalized on our ward for 13 years. During the previous 3 months, his aggressive behavior had gradually increased, resulting in daily physical aggression against either himself or staff members that led to occasional injuries (his mean level on the Overt Aggression Scale was 23). Mr. C was placed on a regimen of cyproterone acetate, increased to a dose of 300 mg/day. His other medications (haloperidol, 20 mg/day; sultopride, 2 g/day; lorazepam, 10 mg/day) were continued. His aggressive behavior was brought completely under control within 8 weeks, but his hallucinations and delusions worsened. The dose of haloperidol was increased to 30 mg/day in order to control the psychotic symptoms. The improvement has been maintained for 10 months, and Mr. C did not relapse when cyproterone acetate was gradually discontinued 3 months ago.

All three patients responded to treatment with cyproterone acetate within 3–4 weeks, whereas other treatments had previously been unsuccessful. No major side effect except moderate weight loss in two cases was encountered in these patients. Plasma testosterone levels remained in the normal range.

Cyproterone acetate may be a promising treatment for some male patients whose aggressiveness is unmanageable by conventional methods, and it would have an advantage over medroxyprogesterone acetate, which can induce important side effects. Additional studies of violent patients are required to confirm these preliminary results.

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## Possible Interaction Between an MAOI and "Ecstasy"

SIR: Harvey Sternbach, M.D. (1) recently reviewed the serotonin syndrome and recommended a heightened awareness of agents that may induce such a state. I would like to report a case in which a patient on a regimen of a monoamine oxidase inhibitor (MAOI) plus lithium seemingly developed the serotonin syndrome when exposed to 3,4-methylenedioxymethamphetamine (MDMA), a drug of abuse referred to as "Ecstasy." A review of the literature yielded one other reported case of a similar interaction (2).

> Ms. A was an 18-year-old woman with bipolar disorder who was treated with lithium carbonate, 1200 mg/day (average serum level=0.7–0.9 meq/liter), and phenelzine, 60 mg/day. While at a party, she consumed a glass of juice that was purported to contain four doses of Ecstasy. She shared this with three other friends, who reported only the expected and no untoward effects. Ms. A developed markedly

increased muscle tension within 15 minutes and was transported to an emergency room. She was described as comatose and tremulous, with decorticate-like posturing and limited response to deep pain. Her pulse was 150 bpm and shallow, her temperature was 100.5 °F, and her blood pressure was 150/100 mm Hg, with a WBC count of 11,000/mm$^3$. Blood gas analysis suggested respiratory and metabolic acidosis. Her lithium level was 1.2 meq/liter (about 8 hours after her lithium dose) and her creatine phosphokinase level was 394 U/liter. Other laboratory examinations produced unremarkable findings.

One hour after the ingestion, Ms. A was described as delirious and agitated. Five hours after the ingestion, she became fully alert and her muscle tone returned to normal, as did all other clinical and laboratory measurements. There were no obvious causes of lithium toxicity. She was discharged after a 2-day hospitalization and there were no apparent sequelae. The patient's phenelzine was initially discontinued but subsequently resumed after a relapse. She has been essentially asymptomatic since that time.

The clinical effects of MDMA typically begin within half an hour and last 4–6 hours. While chemically related to amphetamines, MDMA seems to affect serotonin neurons preferentially (3). It is believed that MDMA stimulates the release of serotonin from presynaptic nerve terminals, particularly those arising in the dorsal raphe. It is interesting to speculate that MDMA's effect on serotonin was responsible for the clinical syndrome observed. It is worth noting that lithium potentiates the effects of serotonin; however, the previously reported case of a presumed MAOI-MDMA reaction occurred in a patient who had not been exposed to lithium.

In sum, this is the second case report suggesting a toxic interaction of MDMA with an MAOI. At this point, it is prudent to be alert to the dangers of such an interaction.

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### Bleeding, a Side Effect of Fluoxetine

SIR: The common side effects reported for fluoxetine are agitation, headache, and insomnia. During fluoxetine treatment of a patient, we encountered the hematological side effect of spontaneous bleeding, which caused bruises and menorrhagia. These symptoms improved upon discontinuation of the drug and recurred upon rechallenge, indicating that fluoxetine was related to the side effect. In this case report, we present the clinical picture of this patient.

Ms. A, a 40-year-old woman, manifested insomnia, anxiety, suicidal ideation, and loss of appetite that had lasted for a few months. The findings of pretreatment laboratory tests and a physical examination were normal. The patient enjoyed normal physical health, with no history of family or personal bleeding disorder. She was prescribed fluoxetine, 20 mg/day, which was increased gradually to 40 and then 60 mg/day. Her response to the treatment was very good, and she resumed her daily activities. By the end of the month after she began taking fluoxetine, she noticed a heavy menstrual flow, which continued for a few days, but she did not consider it to be abnormal. Two months later, she began developing spontaneous ecchymoses; the largest, on her right thigh, was 12–15 cm in length and 3–4 cm in width. A few days later her spleen was palpable, and laboratory tests revealed that her platelet count was 195,000/mm$^3$, WBC count was 4200/mm$^3$, hemoglobin was 13.3 g/dl, prothrombin time was 12.5 seconds, and partial thromboplastin time was 31.3 seconds. Hence fluoxetine was discontinued. Four days later the ecchymosis was fading and the spleen was no longer palpable. The WBC count was 5,000/mm$^3$, hemoglobin was 12.9 g/dl, platelet count was 131,000/mm$^3$, and bleeding time was 6.5 minutes. About a month later Ms. A became so depressed that she took one 20-mg capsule of fluoxetine for 3 consecutive days. She again developed extensive ecchymosis from knee to hip, encircling from front to back. She became frightened and discontinued the fluoxetine. All her symptoms resolved again.

Yaryura-Tobias et al. (1) reported eight cases of bleeding after fluoxetine therapy. In our patient recurrence of bruises upon rechallenge with the drug provides substantial proof of a drug-related adverse reaction. One should be aware of the possibility of the occurrence of bleeding with fluoxetine.

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### Imipramine and Suicidal Thoughts

SIR: A number of case reports have been published associating fluoxetine (1–3) and desipramine (4) with the development of unexpected, possibly ego-dystonic suicidal ideation. In one (4), subsequent use of amoxapine, trazodone, and nortriptyline was associated with the return of suicidal ideation. While the issue is far from decided, especially given Fava and Rosenbaum's retrospective survey (5) that found emergent suicidal ideation not only with fluoxetine (3.5%) but with tricyclic antidepressants in general (specific drugs unspecified) (3%), I present a case of suicidal ideation which developed while a patient was taking imipramine.

Mr. A, a 59-year-old man, had been treated as an outpatient, from early 1986 to the end of 1988, with imipramine in doses of 150–200 mg/day for chronic back pain and depression. He had presented with passive suicidal thoughts ("Why go on?") and had made a self-aborted suicide attempt 16 years previously. His concurrent medications included sulindac, metoprolol, nitroglycerin, and hydrochlorothiazide. He had been treated with 150 mg/day of imipramine, with remission of his depression and better pain control, until the end of 1986, when the dose was in-

> creased to 200 mg/day in an attempt to relieve what were felt to be remaining depressive symptoms (e.g., disrupted sleep). His sleep improved and his mood continued to be improved, although 5 months later he reported that he had been forgetting things and having nightmares. A repeat blood level determination at this dose was the same as at the lower dose, 221 μg/liter. He was worried that he would "have to stop the imipramine and get worse."
>
> In December 1988, although he still reported good relief of both his depression and his back pain, Mr. A unexpectedly decided to stop his medication. A review revealed that while taking imipramine, and despite feeling less depressed and calmer, he would have "crazy impulses to walk downstairs and do things." These thoughts were dystonic, and he was fearful enough that he gave his gun collection, stored in his cellar, to a relative to hold for him. These thoughts had begun to occur sometime after the dose of imipramine had been raised to 200 mg/day. Although the thoughts came only occasionally, he decided that he would rather deal with his pain than continue to take the medicine. There were no obvious life stressors at the time, and he was ashamed to tell anyone that he was feeling these things. The dysphoric feelings and dystonic suicidal impulses passed after he stopped taking his medicine. There was no associated akathisia or anxiety and no personality disorder (although there were avoidant and dependent traits).
>
> Other negative consequences of imipramine use, which also remitted when Mr. A stopped the drug, were excessive body movements during sleep (to a point where he once jumped from his bed into a wall and hurt himself), an increase in nightmares, thinking less clearly, and curtailing his driving because he felt slowed up in his responses. He reported some intermittent memory concerns which vacillated with the amount of pain he experienced.

Although case reports have described the association of suicidal impulses with desipramine and fluoxetine, to my knowledge this is the first report of an association with imipramine. While caution has been recommended in associating suicidal ideation with antidepressants, physicians must be alert to the possibility of suicidal impulses emerging as a drug effect not only late in a course of treatment but in the context of a positive response to an antidepressant. We must be reminded that whatever the origin of these impulses, attention to the doctor-patient relationship is essential in encouraging a patient to feel comfortable about reporting them, especially in the context of depression, where the patient is often self-effacing.

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## Fluoxetine and Fluvoxamine in PTSD

SIR: The serotonin uptake inhibitors have now become the latest in a long line of medications touted as possibly effective in the treatment of posttraumatic stress disorder (PTSD) (1). Continuing this trend, I wish to report a patient whose PTSD symptoms responded to the serotonin uptake inhibitors fluoxetine and fluvoxamine but not to a wide variety of standard pharmacologic interventions.

> Mr. A, a 41-year-old Vietnam veteran with severe PTSD, was seen regularly for supportive group psychotherapy. Despite inpatient treatment on a specialized PTSD unit and multiple trials of neuroleptics, tricyclic antidepressants, and phenelzine, Mr. A's PTSD symptoms gradually worsened after Vietnam. At the time treatment with fluoxetine was initiated, Mr. A's only medication was diazepam, 80 mg/day in divided doses. Fluoxetine was started to help Mr. A with secondary depressive symptoms, which improved somewhat at a dose of 40 mg/day. At a dose of 60 mg/day of fluoxetine, Mr. A noted moderate improvement in his PTSD symptoms, including a decrease in intrusive memories and nightmares (despite no improvement in his sleep pattern), a reduction in overall anxiety, and a lessened need to avoid cues capable of eliciting the symptoms. Unfortunately, Mr. A also developed severe anorexia. After a 30-lb weight loss over 3 months, fluoxetine was discontinued, with the return, over a matter of weeks, of PTSD and, less noticeably, depressive symptoms. A trial of fluvoxamine, 250 mg/day, was then initiated under a compassionate-use protocol for depression. This intervention resulted in a reduction in both PTSD and depressive symptoms similar to that seen with fluoxetine.

The response of this patient to treatment with two structurally different serotonin uptake inhibitors is certainly noteworthy. It is prudent to note, however, that the history of PTSD is replete with anecdotal reports of pharmacologic treatment successes, largely unconfirmed by general clinical experience or controlled trials. My patient also had depressive symptoms, took other medications, was not followed with structured rating scales or rated by blind observers, and received behavior therapy during treatment, thereby limiting the generalizability of the findings.

In any case, the intent of this communication is not to suggest that the serotonin uptake inhibitors will prove to be a panacea for patients with PTSD, particularly since the case for a noradrenergic diathesis in PTSD has been persuasively drawn. On the other hand, the seemingly robust response of PTSD patients to this class of drugs and the phenomenological similarity between PTSD and obsessive-compulsive disorder does suggest that a serotonergic connection might be profitably explored. One prediction from a serotonergic model of PTSD is that drugs useful in the treatment of obsessive-compulsive disorder may also be useful in treating PTSD. Given the marginal performance of antipanic treatments for PTSD (2), properly controlled clinical trials of serotonin reuptake blockers would seem to be in order.

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## Mania During Hemodialysis: Causal or Casual Association?

SIR: Hemodialysis is listed by Kaplan and Sadock (1) among the causes of secondary mania. However, this is based on scant evidence. I have found nine single case reports of mania during hemodialysis (list available on request), of which only three satisfy the criteria for mania secondary to hemodialysis: 1) a manic syndrome appearing during hemodialysis, 2) no delirium or dementia (to rule out dialysis disequilibrium, uremic encephalopathy, and dialysis dementia), 3) no other organic causes of mania, 4) no past history of affective illness, and 5) no family history of bipolar disorder.

A retrospective study was carried out in the hemodialysis unit of a public hospital in Italy to ascertain the incidence of mania during hemodialysis since the opening of the unit. Case notes were reliable because a case of mania (*DSM-III-R*) would have led to psychiatric consultation, which would appear in the notes. I found 30 cases of acute renal failure (21 male patients and nine female) and 103 cases of chronic renal failure (62 male patients and 41 female). In the chronic group 51 patients had died and 52 were still alive. They had started hemodialysis at a mean age of 55 years. The mean age at death was 61 years. The mean age of the patients still alive was 60 years. Patients with acute renal failure were treated for a total of 446 days. Patients with chronic renal failure were treated for a total of 492.6 person-years.

I found only one case of mania, which did not meet the criteria for mania secondary to hemodialysis. In this patient with chronic renal failure, whom I have previously described (2), mania had started weeks before the beginning of the first hemodialysis session, soon after abrupt nicotine withdrawal. During hemodialysis the clinical picture worsened, with the appearance of psychotic symptoms. The incidence (new cases per year) of mania is 1.2/100 for men and 1.8/100 for women (3). I expected to see, for 492.6 person-years of hemodialysis, between five and eight cases of mania; I found only this one.

One possible explanation is that the mean age at the start of hemodialysis was 55 years. The mean age at onset of mania is 30 years (3). However, onset of mania in old age is not unusual (26% of cases) (4). If hemodialysis induced mania, one would expect many more than nine case reports, since over 90,000 patients have undergone hemodialysis in Europe alone. My results suggest that there is no causal relationship between mania and hemodialysis.

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## Folie à Deux Involving a Dog

SIR: Folie à deux, or induced psychosis, is a paranoid delusional system that appears to have developed in an individual as a result of a close relationship with a person who has an established delusional system. Induced psychosis is rare (1). I report a case in which an elderly psychotic woman involved her dog in her deluded behavior, so that the dog itself developed bizarre behavior.

> Ms. A, an 83-year-old widow who had lived alone for 15 years, complained that the occupant of an upstairs flat was excessively noisy and that he moved furniture around late at night to disturb her. Over a period of 6 months, she developed delusional persecutory ideas about this man. He wanted to frighten her from her home and had started to transmit "violet rays" through the ceiling to harm her and her 10-year-old female mongrel dog. Ms. A attributed a sprained back and chest pains to the effect of the rays and had become concerned that her dog had started scratching at night when the ray activity was at its greatest. For protection, she had placed her mattress under the kitchen table and slept there at night. She constructed what she called an "air raid shelter" for her dog from a small table and a pile of suitcases and insisted that the dog sleep in it. When I visited Ms. A at her home, it was apparent that the dog's behavior had become so conditioned by that of its owner that upon hearing any sound from the flat upstairs, such as a door closing, it would immediately go to the kitchen and enter the shelter. When restrained in the living room, the dog reacted to noises from upstairs with agitated barking directed at the ceiling. Ms. A had no previous psychiatric history, and apart from bilateral sensorineural deafness, there was no physical abnormality. A diagnosis of late paraphrenia (*ICD-9,* 297.2) was made. She had no insight and refused admission to a psychiatric facility.

The behavior of Ms. A's dog cannot be considered as delusional but rather as behavioral responses conditioned by the owner's delusional beliefs and behavior. True induced psychoses are rare, but abnormal behavior in the nonhuman companions of the mentally ill is probably common but unrecognized.

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## Antisemitism and Jung's Concept of the Collective Unconscious

SIR: Most (orthodox) psychiatrists and psychologists have never wholeheartedly accepted Jung's ideas of the collective unconscious psychic life. They have, however, not been able to explain the mechanism of intergenerational transmission, through which tendencies such as antisemitism remain virulent. The reasons for the persistence of such irrational and destructive social phenomena as antisemitism urgently need to be dealt with, and Jung's approach could prove useful. As is generally known, Freud's concept of the unconscious is a purely individual one, at least in its definite, concrete appearance. Jung, in contrast, described a kind of unconscious that is common to all humans. The entities that he designated as archetypes are primarily of a religious nature. The manner in which they are transmitted from generation to generation eludes rigorous experimental analysis. Jung once wrote of a "precipitation from the primeval ancestors," and this kind of rather metaphysical explanation can be frequently encountered in his works.

Of course, mechanisms of genetic transmission (i.e., the inheritance of factors that cause disease or certain types of behavior) can be much more precisely defined, but it would be a mistake to try to confine psychology and psychiatry within the straitjacket of the strict scientific paradigm.

In any case, a thorough discussion of the intergenerational aspect of phenomena such as antisemitism would be desirable. Here Jungian ideas could prove helpful; for example, one could use Jungian analysis to find "negative archetypes" such as antisemitism or xenophobia. Of course, every other approach (Friedrich Hacker, Sigmund Freud) could also be applied.

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### Monitored Conditional Release of Persons Found Not Guilty by Reason of Insanity

SIR: The April 1991 issue of the *Journal* contained an article about persons found not guilty by reason of insanity (1). Our findings (2) are similar to the conclusions of that review.

Before 1978, crime relapses of offender patients discharged from security hospitals were very uncommon in Finland. The previous Mental Health Act of Finland (1952) included conditional release. In 1977 the Act was changed. All possibilities of setting terms for offender patients during the outpatient period after hospitalization were abolished, and outpatient care became completely voluntary. We have found out about numerous relapses since then. Up to the end of 1989 we had obtained data on seven homicides and eight other serious violent crimes. The relapses into crime occurred 1.7 years after discharge, on the average. The total number of offender patients discharged from Niuvanniemi Hospital (Department of Forensic Psychiatry) between the years 1978 and 1989 was 258. Thus, the relative frequency of relapses was remarkably high. For discharged offender patients, during the first year outside the hospital, the risk of homicide was about 800 times higher than it was among the general population. We are now finishing our follow-up study because the Act was changed again in 1991.

Contrary to the findings about predicting dangerousness in the review we have cited, we found some predictors. In Finland we have remarkable opportunities for follow-up studies because according to Finnish law, forensic psychiatrists not only give expert testimony in court cases but are also responsible for psychiatric care of offender patients. With a few exceptions, the crime relapses have occurred among patients who were without insight, had neglected to contact a mental health center, and had rejected their psychiatric medication. Relapse into crime was associated with abuse of alcohol in 13 cases, which may have some link to the role of serotonin in aggressive behavior (3).

The risk of crime relapse among offender patients who have previously committed violent crimes is very high. Our opinion is that some terms or requirements are needed during the outpatient period in order to prevent dropping out of treatment.

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### Bone Loss in Patients With Anorexia Nervosa

SIR: Juanita J. Salisbury, Ph.D., and James E. Mitchell, M.D., in their review of bone mineral density in women with anorexia nervosa (1), discussed the relative importance of factors that correlate with bone loss. They commented that duration of amenorrhea, reflecting caloric deprivation and concurrent depression of estrogen levels, was important in the development of bone loss, but this only contributed an average of 25% of the variance to bone loss in the studies reviewed. They concluded that "future experiments need to address more precisely the roles of calcium intake, exercise, estrogen, and other hormones" in women with anorexia nervosa.

We evaluated retrospectively the longitudinal risk factors for bone loss in a controlled study of 69 female adult outpatients with past or current anorexia nervosa (2, and P.J. Hay et al., manuscript submitted for publication). Weight and menstrual histories were assessed by semistructured interviews, and current and lifetime exercise and dietary calcium levels were quantified by detailed questionnaires and interviews. Serum hormones were measured and total calcium assays done. Our results support those of others who have found significantly lower bone density in women with anorexia nervosa than in control subjects. A multivariate analysis of risk factors for bone loss found that the best predictor of bone loss on stepwise multiple regression analyses was duration of anorexia nervosa (19% of the variance, $p<0.001$). A second regression analysis was done with duration of anorexia nervosa removed from the analysis. In the second analysis, duration of amenorrhea explained 18% of the variance ($p<0.001$), and duration of an inadequate calcium intake in adolescence explained 7% of the variance ($p=0.02$). There was no evidence that regular exercise and adequate dietary calcium prevented bone loss related to prolonged periods of low weight and amenorrhea in these subjects.

This is the first study to have found an association between dietary calcium in adolescence and adult bone loss in women with anorexia nervosa, and it supports the finding of Sandler et al. (3) that in postmenopausal women, adequate adolescent dietary calcium is important to adult bone density. However, while adequate dietary calcium is important in postpubertal bone accretion, it will not prevent later bone loss due to a relative estrogen deficiency. Our detailed assessment of exercise and dietary calcium levels suggests that modification of lifestyle factors such as exercise and dietary calcium intake are unlikely to improve bone density when there is continued low weight and amenorrhea. We support the conclusion of Drs. Salisbury and Mitchell that the most important aspect of treatment is to reverse weight loss and obtain resumption of normal menstruation, while the role of other treatments, such as oral estrogen, remains unproven.

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## Mania in AIDS and Syphilis (Paresis)

SIR: Recently, Karl Kieburtz, M.D., and associates reported on eight AIDS patients with mania (1). The report included detailed data from a variety of neuropsychological tests and CSF and magnetic resonance imaging (MRI) studies but nothing about the patients except age, race, sex, and homosexual orientation. Five of the eight had depression following the initial HIV diagnoses. The mania improved with lithium and neuroleptics, but the course of illness was not typical for bipolar disorder because of persisting cognitive impairment. Unfortunately, there was no follow-up of the eight patients. The authors suggested, as have others, that the mania was a secondary disorder associated with rapidly emerging cognitive decline due to increased cerebral viral activity.

Certainly, the mania is "associated" with AIDS, but it is primarily a psychobiological reaction, and a fairly adaptive one at that, in the face of absolute hopelessness and certain death, rather than directly related to and "caused by" the underlying neuropathology as revealed in MRI studies and autopsy reports. The fact that five of the eight patients had a prior depression, (not an unusual finding) lends support to the possibility that the mania was a more adaptive response—a denial of impending disintegration. Better to be "Jesus" or "God" than face the dreadful reality of abandonment and death.

A few months ago, in a clinical teaching conference, I interviewed a 38-year-old homosexual man with AIDS who had been admitted to the hospital in a manic state. He was grandiose (with delusions that he, like Jesus, had started a new religion), euphoric, hyperactive, and irritable but had no cognitive impairment on clinical and psychological testing. When faced with the seriousness of his disease, his eyes filled with tears and he said, "I cry myself to sleep every night," then quickly became manic, exclaiming that he was looking forward to "joining God, my father, in paradise." He was treated with lithium and neuroleptics and after 4 weeks was discharged as improved. After a week he relapsed and was admitted to another hospital, given ECT, and once again discharged as improved. Currently, he is doing well.

After the interview I was struck by the similarity of this patient to grandiose paretic patients I had seen 50 years ago. Amazingly, I remembered some articles published in 1941 (first from the Menninger Clinic) on the treatment of paresis with metrazol and ECT. I reviewed these articles published between May 1941 and November 1945 (2, 3). Most were favorable, a few not. The first report of the treatment of paresis by penicillin appeared in December 1945, following which treatment by ECT stopped.

In both CNS syphilis and AIDS, the basic disorder is the dementia. Depression is the most frequent of the psychiatric syndromes, while mania, although most striking, is relatively infrequent (4, 5).

The paretic patients treated with ECT also received fever and chemotherapy, similar to the treatment of AIDS with zidovudine (AZT), ECT, and neuroleptics. But today we are more aware of the shame, guilt, humiliation, and anger of AIDS patients. Probably, these feelings existed in paretic patients too, but were ignored. When the "penicillin" for AIDS appears, the manias along with the treatment by ECT and "modern chemotherapy" will disappear. History repeats itself.

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## Stress and HIV Infection

SIR: Ronald C. Kessler, Ph.D., and his colleagues (1) found no relation between certain stressful life events and either decrease in percent of CD4 cells or symptom onset in HIV infection. While we agree with the general spirit and conclusions of this careful study (2), we wonder whether the authors might wish to reconsider their statement that "intervention programs designed to help people with HIV infection cope with stress are unlikely to be useful in prolonging health."

First, stressful life events must be distinguished from "stress" (3), which was not reported. Second, some studies suggest a relation between emotional distress and behaviors that transmit HIV (4). Interventions that reduce distress might therefore prolong health within the community as a whole. Third, reduction of emotional distress in HIV-positive individuals (5) might help increase compliance with effective maintenance medications and, more generally, might increase hope and seeking early medical intervention for treatable opportunistic infections and tumors. Studies of patients with other medical illnesses (6) suggest that further investigation is warranted before concluding that psychotherapeutic interventions for those with HIV infection will not prolong their health.

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## Dr. Kessler and Colleagues Reply

SIR: We thank Dr. Perry and associates for their thoughtful comments. Our conclusions might indeed be altered by a consideration of a broader series of stresses. In particular, several studies (1–3) suggest that chronic stress is more strongly related than life events to a variety of mental health outcomes. There is considerable controversy, though, about the validity of currently available scales to measure chronic stress (4), so we chose to measure only major life events in our study. We also agree that intervention programs designed to help people manage stress might successfully reduce behaviors that transmit HIV, but evidence on this possibility is scant.

Dr. Perry and colleagues note an association between emotional distress and risky sexual behaviors. However, there is little known about the mechanisms involved in this association and virtually nothing known about the role of stress. We carried out some new analyses on this issue in the Chicago Multicenter AIDS Cohort Study/Coping and Change Study data after seeing the letter from Dr. Perry and associates and discovered no relation between stressful life events and risky sexual behaviors. This result is not inconsistent with the possibility that intervention programs might influence behaviors that transmit HIV or, as suggested in the third point of the letter, that such programs might encourage active help seeking and compliance with medication regimens. Our failure to find an effect of stressful life events on behavior change does suggest, though, that the recent occurrence of a major life event is not a good indicator of risk status. Individual differences in emotional reactivity are more likely intervention targets. Naturalistic research on these possibilities, ideally including a broader assessment of stress than was used in our work, is needed to help identify the populations most in need of interventions.

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## Nicotine Gum in Tourette's Disorder

SIR: With reference to "Nicotine Potentiation of Haloperidol in Reducing Tic Frequency in Tourette's Disorder" by Brian J. McConville, M.D., and associates (1), while I appreciate the theoretical reasons for using nicotine to ameliorate tics, methodological flaws in the study detract from the validity of the authors' conclusions.

They stated that "a placebo gum that tasted similar to the active gum was not available." Consequently, in the control situation the subjects did not chew gum. However, if gum had been used as a placebo, it would have "blinded" the independent raters and controlled for the effect of chewing per se on tics, adding to validity.

Chewing may have had an independent effect on facial and/or vocal tics, either directly or indirectly, through general relaxation. No indication of the differential effect on facial and/or body tics was given.

The method of interviewing patients over 2 hours could have been better standardized. No controls were used to see how tics varied naturally over the time period (perhaps the subjects relaxed over the first half-hour). Patients could have been filmed performing set tasks such as reading, computing, or sitting silently, which has been shown to have excellent reliability and validity in measuring change (2). Although interviewers "avoided topics of known stress" at interview, there must have been considerable interpatient and intrapatient variation that was avoidable.

While the findings of Dr. McConville and associates are of interest and may suggest further research, the points I have mentioned, added to the small number of patients (N=10), make statistical analysis irrelevant and misleading.

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SIR: We were very interested in the report by Dr. McConville and associates concerning the effect of chewing nicotine gum on tics in patients with Tourette's disorder treated with haloperidol. Anything that could reduce the dosage of neuroleptics and their side effects is an important area of study. We have a few questions about the report and would appreciate the authors' comments.

First, since the authors did not do a placebo gum chewing trial, could they address the possibility that gum chewing itself may have been responsible for the reduction in tics? Brill (1) reported the case of a 12-year-old boy with Tourette's disorder whose tics were reduced by gum chewing. Apparently, this also occurs with facial dystonias (1). It has been our experience with many patients that repetitive, low-level, apparently voluntary movements are utilized by Tourette patients to discharge energy and ease the need for tics. Children who chew gum report that this decreases facial tics. Those who tap their hands feel that it lessens arm and shoulder tics. Patients who shake their legs feel that they do it to prevent large, embarrassing leg jerks. We realize that it is difficult in Tourette's disorder to distinguish a tic from a compulsion, as well as voluntary from involuntary, or even unvoluntary, movements.

Second, in table 1, for most patients tics were less frequent after gum chewing than at baseline. However, in all but two cases, there was an increase toward the baseline number after gum chewing stopped. Would the authors postulate that the nicotine potentiation of haloperidol decreases so quickly, or could this point to a possible gum chewing effect? The authors stated that the effects were seen dramatically within 3 minutes. Does the time action of nicotine gum chewing and haloperidol potentiation fit this pharmacologically?

Our final concern is a clinical one. With the known toxicity and addictive potential of nicotine and its questionable safety in children, adolescents, and pregnant women, we feel that the authors should have more clearly listed potential harmful effects (*Physicians' Desk Reference,* 1991). A pilot study such as this could encourage people to try this treatment despite the authors' general cautions. Potentially harmful effects should be listed specifically.

We are encouraged that the authors are continuing to study this fascinating topic. We look forward to their comments.

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### Dr. McConville and Dr. Norman Reply

SIR: We have reviewed with great interest the letters from Dr. Rickards and Dr. Arevalo and associates with regard to our article. These letters certainly indicate the wide interest in any potential new treatments for Tourette's disorder.

A placebo gum with a taste similar to that of the nicotine gum was not available to us during these studies. However, such a gum was subsequently made available, and we have recently conducted a study that compared nicotine gum to placebo gum. This overcomes the problems with blinding and also controls for the independent effects on facial and vocal tics through general relaxation while chewing. These data are now being considered for publication. We were aware of the interesting paper by Brill, and we have had similar clinical experiences. However, although gum chewing might be independently relaxing, the subjects chewed gum for only 30 minutes during the 2-hour period. The effects on tics (both facial and body) were apparent during the two subsequent 30-minute periods when no gum was being chewed. In our analysis of results, different tics were observed from videotapes of each patient, with independent assessments made of each type of tic. No differential effect was noted in the responses of facial versus other body tics.

Interpatient variation occurred, but in the study design each patient served as his or her own control. Intrapatient variation during the measurement period was minimized by quiet conversation, avoiding stress, with an interviewer who was familiar to the patient. Our earlier attempts at having children read silently or perform routine tasks over a 2-hour period had variable success, in part because of comorbid attention deficit hyperactivity disorder symptoms in subjects with Tourette's disorder, which we described earlier (1). The statistical analyses (one-within repeated measures analysis of variance) were appropriate for this study, and since the effect noted was large, significant differences were obtained with 10 subjects.

We observed some diminution in tic frequency and severity 3 minutes after subjects began chewing gum, and the effect was robustly present at 10 minutes. Benowitz et al. (2) have indicated that there was a sharp increase in average blood nicotine concentration while subjects chewed 2-mg nicotine gum for 20 minutes. These data imply that blood concentrations of nicotine achieve a physiologically relevant level within a time frame consistent with our observations. Furthermore, these authors reported a subsequent fall of approximately 50% over the next 40 minutes. This finding also correlates with our observed increases in tic frequency and severity over the 60 minutes following gum chewing.

We agree with the concern of Dr. Arevalo and associates about the toxicity and addictive potential of nicotine. We had listed such potential harmful side effects more fully in an earlier version of the paper and stated in the final condensed version that we do not recommend the uncritical and excessive use of nicotine.

We are pleased that both letters note that our data are interesting and suggest further research. A number of the suggestions have already been incorporated into our latest studies. We thank the writers for their comments and suggestions and look forward to further studies in this interesting area.

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### Seven-Day Mood Cycles

SIR: In their study of mood variance in depression, Donald P. Hall, Jr., M.D., and colleagues (1) demonstrated an ultradian mood rhythm in both depressed and nondepressed subjects, with the former subjects showing ultradian cycles of greater amplitude than did the latter. The authors concluded that "repeated assessments of mood at different times of the day may be necessary to obtain an accurate impression of a patient's mood state." Over the past several years, my research (assisted by L. Crosby, J. Trynan, and M. Palmerino) has shown analogous findings in the weekly mood cycles of certain predisposed individuals. Such "circaseptal" rhythms have been suspected in several physiologic parameters, but have come to light only recently (unpublished manuscript by F. Halberg, October 1984).

In a survey completed by 111 individuals, we assessed the presence and severity of Sunday-Monday dysphoria, often termed the "Monday blues." Thirty-one of the respondents had previously answered a query seeking individuals suffering from the Monday blues. Eighty other individuals were selected at random from the Boston-area telephone directory. On the basis of the frequency of Monday blues indicated by the respondents (varying from every week to once every couple of months), we defined a high-frequency blues group. In a one-way analysis of variance design, we found that this group was much more likely to experience their weekly dysphoria as qualitatively different from symptoms experienced on other days of the week than were the low-frequency sufferers ($F=10.05$, $df=3, 91$, $p<0.0001$). The high-frequency group was also more likely to say that their weekly dysphoria affected their jobs or personal lives ($F=2.65$, $df=3, 91$, $p<0.05$). Other research (Pies, unpublished data) suggests that a high frequency of circaseptal dysphoria is correlated with a past history of depression or other emotional problems. The work of Dr. Hall and associates and the findings I have reported suggest that both ultradian and circaseptal rhythms should be considered when evaluating a patient's mood state.

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### Dr. Hall Replies

SIR: Dr. Pies offers an interesting observation regarding 7-day mood cycles. However, it is not clear from his letter whether he is suggesting that these 7-day cycles represent an endogenously controlled rhythm or a response to cycles of environmental stimuli. It is possible that these "circaseptal" cycles represent responses which are predominantly affected by environmental variables. Ultradian mood cycles, however, do not appear to be correlated with repeating environmental stimuli and probably reflect underlying physiological cycles. The greater amplitude of ultradian rhythms that we observed in depressed persons may represent a dysregulation of neurotransmitter output, leading to a more variable, high-amplitude fluctuation of intradaily mood. It has been suggested that similar phenomena are related to bipolar disorder (1) specifically and affective disorders (2) in general.

With the data presented by Dr. Pies, we can not be certain what factors contribute to the 7-day cycles. However, a history of Monday blues may indicate a susceptibility to depression, and we concur that this may be a useful symptom to consider in the evaluation of depression.

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### Magnetic Resonance Imaging in the Diagnosis of Dementia

SIR: The report by Peter V. Rabins, M.D., and associates (1) was cited by the authors as the first of its kind concerning cortical magnetic resonance imaging (MRI) changes in elderly depressed patients. This line of investigation is laudable and integral to the elucidation and characterization of the neuroanatomic correlates of clinical phenomena seen daily by practicing clinicians.

However, in the Results section, the authors stated, "There were no differences between the depressed patients and the patients with Alzheimer's disease on any measure" (of the MRI). Furthermore, no stratification of patients was done according to Mini-Mental State examination scores to separate depressed persons with accompanying cognitive decrement and those without (i.e., the "pseudodemented"). Therefore, except for the conclusion that individuals with illness (in this case, the depressed elderly and those with Alzheimer's disease) differ similarly in their MRI scans from control subjects, I am curious about how, on the basis of the authors' findings, MRI would assist in the differential diagnosis of the clinically demented (i.e., individuals with Alzheimer's disease versus the pseudodemented depressed elderly).

The authors' topic is most exciting, and I share their tacit assumption that these questions may be more readily answered with newer and more advanced cortical imaging techniques.

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### Dr. Rabins and Associates Reply

SIR: Dr. Dentino raises a question about the diagnostic implications of the imaging abnormalities we reported in elderly depressed subjects. To our knowledge, no imaging technique has yet demonstrated adequate sensitivity and specificity for use in making a diagnosis of any psychiatric disorder. Therefore, the clinical assessment remains the gold standard, with imaging findings as one of the factors to be considered. Dr. Dentino also raises questions about imaging distinctions between individuals with the dementia syndrome of depression and cognitively normal depressed persons. We have addressed this in studies using CT head scans (1, 2) and found that patients with primary major depression and Mini-Mental State examination scores below 24 have lower CT attenuation numbers than patients with major depression who have Mini-Mental State scores above 24.

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## Proposed Model for Self-Injurious Behavior

SIR: The excellent review of self-injurious behavior by Ronald M. Winchel, M.D., and Michael Stanley, Ph.D. (1) makes clear that we have no unifying theory or model for self-injurious behavior. Rather, it is approached from a variety of perspectives, including the affected population, putative psychodynamic issues, and possible neurotransmitter abnormalities. I wish to propose a heuristic model in which two broad types of self-injurious behavior are distinguished.

In type I, onset is usually during early adulthood, and the self-injurious behavior entails one or more isolated but serious acts. The lesion is frequently "ablative" (e.g., autocastration) and associated with either a circumscribed somatic delusion or a severe identity disturbance. Such self-injurious behavior is generally seen in schizophrenic or other psychotic patients. I hypothesize that a primary excess of dopaminergic function is the principal neurotransmitter abnormality in type I and that both $D_2$ and $D_1$ receptors are implicated (possibly with $D_2$ dysfunction predominant). Dopamine agonists would tend to worsen this type of self-injurious behavior, which may respond to conventional antipsychotics.

In contrast, type II has its usual onset in childhood or adolescence, in association with a variety of neurodevelopmental and character disorders, for example, Tourette's disorder, autism, attention deficit hyperactivity disorder, and Lesch-Nyhan syndrome. Some individuals with borderline personality disorder and "obsessive spectrum" disorders also fit the type II pattern. Self-injury is usually chronic, repetitive, and "irritative" rather than ablative. The lesion is usually not "symbolic" (as in autocastration) but is associated with a more general relief of tension, anxiety, or anger. Clear secondary gain is sometimes involved, as when a patient with borderline personality disorder engages in low-lethality wrist cutting to delay discharge from the hospital. Although endogenous opiate dysregulation may be involved, I postulate two principal neurotransmitter abnormalities in type II self-injurious behavior: a primary dopamine deficiency which, over time, may lead to secondary dopamine receptor hypersensitivity and/or a dysregulation of serotonergic systems (1–4). $D_1$ receptors—possibly in nigrostriatal more than in mesolimbic tracts—are involved preferentially. Treatment with either dopamine agonists or antagonists may be helpful, depending on the point of "transition" between primary dopamine deficiency and dopamine receptor hypersensitivity. Serotonergic agents (e.g., fluoxetine, clomipramine) are also helpful in this type, particularly in patients with "obsessive spectrum" symptoms such as trichotillomania (5).

I propose this dichotomy as a spur to the development of a unified theory of self-injurious behavior and not as the definitive statement on this complex condition.

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## Dr. Winchel and Dr. Stanley Reply

SIR: The possibility of dopaminergic and serotonergic dysfunction among individuals who self-mutilate—as we discussed in our review and is emphasized again by Dr. Pies—is a reasonable basis from which to pursue investigations of self-injurious behavior. We agree on the value of an approach that cuts across diagnostic categories and is based on characterization of specific common behaviors, i.e., a dimensional rather than a categorical view. The utility of this approach is exemplified by the finding that suicidal behavior is associated with altered serotonergic function. The evidence that disrupted serotonergic function is independent of primary diagnosis and is associated with suicidal behavior per se demonstrates that neurophysiologic markers may be associated with individual behaviors rather than with traditional syndromal categories.

A similar finding (that self-injurious behavior across diagnoses is associated with a consistent biological marker) would indeed set the stage for a "unified field" theory of such behavior. While Dr. Pies's ambition in suggesting the framework for constructing such a theory is admirable, we would argue that it is still too early to do so. Until self-injurious behavior is further characterized, patient groups are still distinguished more by the differences in their patterns of self-mutilation than they are by what is common. For example, Dr. Pies suggests that the type II behavior may be characterized as "repetitive," yet a patient with a character disorder might repeat self-injurious behavior several times in a year, whereas among the developmentally disabled, it may occur several times in an hour. Until we have a firmer basis for behavioral classification of self-mutilation, it will remain difficult to make meaningful comparisons of biochemical findings.

Attempts to impose order on the chaos of disparate findings in self-injurious behavior may have the benefit of guiding a developing research agenda regarding this behavior. However, the available data, in our view, do not yet support any general unifying theory.

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## Serotonin and Effect Sizes of Antiobsessive Agents

SIR: Michael A. Jenike, M.D., and associates recently reported results on the use of pharmacologic agents that inhibit serotonin uptake in treating obsessive-compulsive disorder (1). They conducted meta-analyses to determine effect sizes by subtracting the endpoint mean from the baseline mean and dividing this by the standard deviation at baseline. They found that clomipramine was most effective in producing antiobsessive activity: effect size=1.53 (N=13). It was followed by fluoxetine, 1.34 (N=61); fluvoxamine, 1.09 (N=18); and sertraline, 0.80 (N=10). This outcome was consistent with their earlier finding that a controlled trial of clomipramine produced a greater effect size than an open trial of fluoxetine (2). These results led them to conclude that less selectivity in inhibiting serotonin uptake may be associated with a greater effect size.

We decided to do a similar analysis of our recently reported data on subjects who had received buspirone or clomipramine (3). We conducted a meta-analysis of these two groups of patients with obsessive-compulsive disorder (each N=9), using the same formula to compute effect size. Obsessive-compulsive symptoms were assessed with the Yale-Brown Obsessive-Compulsive Scale in all of the studies, and the effect sizes were based on this instrument, as in the work of Dr. Jenike and colleagues. The effect size for clomipramine was 1.50, similar to that reported by those authors. Also of interest, however, was our finding that the effect size for buspirone was 1.42, higher than that reported by Dr. Jenike and associates for fluoxetine, fluvoxamine, and sertraline. This is particularly interesting in light of a report by Dr. Jenike and Dr. Baer (4) that buspirone was ineffective in an open trial in patients with obsessive-compulsive disorder.

Possible interpretations of this result must be tempered by the fact that the numbers were small in both buspirone studies (N=9 in ours and N=10 in Jenike and Baer's) and by the fact that effect size may be influenced by the baseline level of symptoms as well as the standard deviations within the sample. It is also hard to equate the relative potency of the serotonin activity of buspirone with that of the agents that Dr. Jenike and associates reported on (clomipramine, fluoxetine, fluvoxamine, and sertraline), because unlike these agents, buspirone is a partial serotonin$_{1A}$ agonist and not a serotonin uptake inhibitor.

Recently, Hewlett et al. (5) reported that clonazepam had shown some efficacy in treating obsessive-compulsive disorder. Clonazepam, while it also affects serotonergic transmission, does not do so by uptake inhibition (5). Thus, this preliminary finding would seem to support the notion that other aspects of the serotonin system besides uptake inhibition might be involved in antiobsessional efficacy (1) and warrants further exploration.

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## A Serotonergic Component in Splitting?

SIR: The conclusion of John G. Gunderson, M.D., and Katharine A. Phillips, M.D. (1) that the borderline syndrome is linked with serotonergically mediated impulsiveness may be a testable conceptual bridge between the psychoanalytic and biological models of severe pathology. One of the consequences of the defense of splitting which is found in borderline and other patients is an impulsiveness that derives from this defensive failure to invest people with human (i.e., whole object) qualities that can be empathized with. Instead, they are only experienced as inanimate (i.e., part objects) to be controlled and collected. This trance-like reduction of others and one's self and body into a "thing" status that is without memory limits one's relatedness to them to impulsive and addictive monotony and reduces self-empathy into compulsive food binging and/or self-mutilation. Such self-abusive enactments derive from this impersonal, split sense of self that only recognizes one's body as a foreign entity, similar to its being one's own imaginary companion.

The action and somatic impulsiveness that the defense of splitting leads to is the very same symptom that one regularly reads is responsive to fluoxetine in bulimia, kleptomania, trichotillomania, etc. It is the underlying frenzy of the impulsiveness, independent of its content, that is reduced by the new antidepressants. This may be due to their ability to correct the underlying serotonergic deficiency that contributes to the defense of splitting and its manifestation in various forms of addictive impulsiveness.

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## Response of Schizophrenic Patients to Benzodiazepines

SIR: The extensive review article by Owen M. Wolkowitz, M.D., and David Pickar, M.D. (1) on the use of benzodiazepines in the treatment of schizophrenia raised a number of possibilities to explain the variability and prediction of response. One additional factor that might be considered is the possibility of alcohol abuse and its subsequent withdrawal symptoms. Recent studies (2) indicate that schizophrenic patients have a lifetime prevalence of alcohol dependence/abuse of 47%. Patients with comorbid alcohol use and schizophrenia would experience more dysfunction and more frequent hospitalization than schizophrenic patients without alcohol (or other substance) abuse. This would then bias any acute treatment setting toward a higher percentage of alcohol-abusing/dependent patients with schizophrenia, whose symptoms would be improved when the subsequent withdrawal or cravings were treated with benzodiazepines. This would result in lessening of agitation, restlessness, tension, hostility, irritability, and perhaps also the delusions and hallucinations associated with an overstimulated state. In addition, those whose withdrawal symptoms were thus cleared might then show a lessening of effects over the following weeks as the withdrawal symptoms diminished.

It would be most interesting to see whether treatment based on the separation of alcohol-using schizophrenic patients from abstinent ones resulted in clarification of the noted variability in response and would provide a good predictor of response as well.

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## Dr. Wolkowitz and Dr. Pickar Reply

SIR: We thank Dr. Dreher for his thoughtful comments on our review article. He has highlighted one of the most perplexing issues in the evaluation of the double-blind study literature on benzodiazepine efficacy in schizophrenia, namely, the variability and prediction of response. We agree that patients who have recently engaged in alcohol or other sedative/hypnotic abuse or who present during drug withdrawal may benefit from benzodiazepine treatment. Such benefit, as Dr. Dreher points out, would be nonspecific and would be due primarily to amelioration of withdrawal symptoms.

While such circumstances occur with some frequency in clinical settings, the double-blind research studies we reviewed generally carefully screened out patients with significant recent alcohol abuse as well as patients in the midst of alcohol or sedative/hypnotic withdrawal. Thus, we believe that such an explanation is unlikely to account for the variability in response seen in these studies. Indeed, we have been struck, in our own studies, by the lack of reliable clinical predictors of response.

Since our review article was written, we have studied an additional 23 patients with schizophrenia (screened to rule out substance abuse for at least 1 year) for whom either placebo or alprazolam was added to stable neuroleptic regimens. We have continued to observe both significant antipsychotic effects of alprazolam and considerable interindividual variability, with 42% of individual patients showing decreases in psychotic symptoms greater than the mean decrease (+2 SD) seen in the placebo group.

We have previously suggested that schizophrenia is a heterogeneous disorder and have suggested several strategies for interpreting ambiguous or inconsistent data obtained in pharmacologic trials in this population (1). We hope that by delineating individual characteristics which underlie treatment responsivity, we may be able to identify homogeneous (and possibly pathophysiologically distinct) subgroups of patients.

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## Olfactory Hallucination After Intravenous Caffeine

SIR: The article "Caffeine Augmentation of ECT" by C. Edward Coffey, M.D., and associates (1) prompts us to report a case in which the intravenous administration of caffeine seemed to precipitate an aura-like olfactory hallucination.

Ms. A was a 53-year-old woman with a history of psychotic depression, a seizure disorder, and also the possibility of an undiagnosed degenerative brain disorder. She had had several generalized seizures within the last several years but no complex partial seizures. Neurologic evaluation included a normal EEG, a CT scan showing a lacunar infarct in the left external capsule, and a normal lumbar puncture. She had been treated with carbamazepine for her neurologic and psychiatric illness. When this medication was withdrawn, she had a series of generalized convulsions within hours. She had never described any aura prior to her seizures.

Since Ms. A's psychiatric illness was refractory to medications, ECT was initiated. Because of concern about precipitating status epilepticus if her carbamazepine were withdrawn completely, she was treated while on a regimen of a lower dose of carbamazepine. Her seizure length was short during ECT (<15 seconds) despite the use of the highest setting on the ECT machine. Accordingly, by the 11th treatment she was given 250 mg of intravenous caffeine sodium benzoate 5 minutes before ECT. This had little effect and the dose was subsequently increased to 500 mg before treatment 13. This had the desired effect of prolonging her seizures to 40 seconds. It is interesting that at the 500-mg dose, 30 seconds after the intravenous injection of the medication, she stated, "I smell something bad." When asked to describe this further, she was unable to do so. The sensation seemed to persist for only several seconds. At the next three treatments, she received 500 mg of caffeine and had exactly the same reaction. After several seconds, she said, "Oh, I smell something funny. Ooh! It's bad." She was clearly distressed by this sensation. When her seizure length again decreased, the dose of caffeine was increased to 750 mg and subsequently to 1000 mg; however, at the highest dose, she did not have the olfactory hallucination.

We believe that this clinical phenomenon represents some effect of caffeine on the medial temporal lobe. Although this patient did not have a seizure aura during her spontaneous seizures, we believe that her smelling an unpleasant odor is analogous to what epileptic patients experience during an "uncinate fit," which is thought to reflect stimulation of the primary olfactory cortex in the medial temporal lobe. This would be in keeping with work by Nakajima et al. (2) and others showing that caffeine induces seizures in rats and may preferentially activate various brain regions, including the medial temporal lobe and olfactory tubercle. Since intravenous caffeine is given to a large number of patients to increase seizure length in ECT (1), it would be interesting to discover whether others experience activation of temporal lobe structures. It is possible that our patient's preexisting epilepsy made her vulnerable to such stimulation and that most patients would not respond this way. Indeed, we have not seen this phenomenon in any of the other patients to whom we have administered caffeine.

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## Conditions Not Attributable to a Mental Disorder

SIR: John M. de Figueiredo, M.D., Sc.D., and associates, in their study on conditions not attributable to a mental disorder (1), found that persons with family problems but without mental disorders constituted about 20% of all individuals (N=382) admitted to an outpatient psychiatric clinic during a 2-year period. The authors suggested that more research was needed on the patterns of use of psychiatric services by individuals with *DSM-III* V code conditions.

I have recently concluded a review of the persons attending our public psychiatric service with all *DSM-III-R* V code conditions and without mental disorders. Using *DSM-III-R* criteria, I reviewed records of all new patients who had attended our service from January to December 1990. I found 490 new patients; only 45 (9.18%) had unequivocal *DSM-III-R* V code conditions without mental disorders, of which 25 (5.10% of total cases) were family problems. Twenty-seven (60%) of these 45 patients had been seen repeatedly by psychiatrists (the mean number of visits was 8.68 during 1 year); 20 patients had been treated with psychotropic drugs (according to my view, inappropriately) and supporting psychotherapy; and two had been referred to a psychologist for cognitive psychotherapy. Reviewing case notes of the last 5 years, I found that attendance for family or social problems had increased gradually (from about 6% in 1986 to 9.18% in 1990). The proportion of patients with *DSM-III-R* V code conditions was similar to that observed in other Italian services (presentation by R. Chiecchio et al. at a conference in Naples, Italy, 1989).

Unlike Dr. de Figueiredo and associates, who found that patients without mental disorders who had family problems were mostly referred by their families, I found that only 26% were referred by their own families, 15% were self-referred, and over 37% were referred by their family doctors or by other physicians. To me this suggests that nonpsychiatric physicians in our region do not have a clear idea of the function of a mental health service. Patients with *DSM-III-R* V code conditions without mental disorders are clearly a heavy burden for psychiatric services, consuming time that could be used more appropriately for more severe disorders; in my study they represent almost 10% of patients seen at least once in 1 year.

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## Dr. de Figueiredo and Associates Reply

SIR: Dr. Mazzoli's findings demonstrate, once again, the need for cross-national and cross-cultural comparisons of the patterns of use of psychiatric services for conditions not attributable to a mental disorder.

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HEIDI BOERSTLER, D.P.H., J.D.
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## Environmental Factors in Psychiatric Disorders

SIR: The article "Genetics and Psychiatry: An Unheralded Window on the Environment" by David Reiss, M.D., and associates (1) provided an important balance of perspective to our understanding of mental disorders. However, it also reflected a somewhat pessimistic view of the contributions of genetics to psychiatry. This has been eloquently commented on by Miron Baron in an editorial in *Biological Psychiatry* (2).

We would like to point out an important potential problem raised by the review by Dr. Reiss and colleagues. Although juxtaposing "genetic" and "environmental" perspectives may be useful for heuristic and research purposes, polarizing the two can appear to create "debates" that are confusing to policy makers and ultimately undercut support for research on mental illness. As Baron noted, "Coexistence and cross-fertilization might be the optimal modus operandi for these two views of psychiatry" (2).

There may be another basis for misunderstanding here. "Genetic" is not a synonym for "biological," nor is the environment equivalent to psychosocial factors. As we made clear in our own article (3), a wide array of psychosocial considerations must be taken into account when considering the potential effects of genetics on psychiatric disorders. While Dr. Reiss and associates acknowledged that biological factors play a part in the environment, these were not given substantial attention. Ultimately, we may find that the neurodevelopmental "environmental" processes at work in utero and in early childhood are of the utmost relevance to psychiatric disorders. This possibility underscores the need for broader-based, integrative research at all levels to understand better the etiology and treatment of these profound and devastating conditions.

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## Involuntary Treatment

SIR: I wish to take issue with the conclusions drawn by Julie Magno Zito, Ph.D., and associates in their study of drug treatment refusal (1). As a frequent independent evaluator of and witness for patients who have been referred for adjudication to obtain orders for involuntary treatment, my experience has led me to quite different conclusions.

The high rate of withdrawn applications ("nearly one-third") for court review of proposed involuntary treatment reported by the authors is certainly confirmed by my own experience. Their conclusion that "the court-driven system . . . is used . . . almost exclusively for cases in which the legal outcome is clear" is contradicted by this evidence. I have found that the most common cause of withdrawal of applications for involuntary treatment has been one also noted by the authors, a lack of belief by the applicant that a "satisfactory decision" (an order for involuntary medication) will result. The application can be used as a coercive manipulation to prod patients into accepting treatment but is withdrawn if challenged, to avoid the negative court decision. Thus, in fully one-third of cases, the outcome may not be a foregone conclusion, and in an additional 8%–9% of cases, the authors noted that applications were denied by the court. When nearly one-half of applications do not result in orders for involuntary treatment, the legal outcome is not at all clear.

Dr. Zito and associates pointed out that the delays in scheduling court hearings (30 days or more) may represent a violation of patients' right to due process, but they then drew the peculiar conclusion that as a result of this, patients should be deprived even further of due process by denying them the right to a court hearing at all! Similarly, their arguments that the inefficiency and costliness of court hearings should result in their discontinuation is discriminatory. The need for sometimes time-consuming court proceedings is not restricted to the psychiatric population, yet no one suggests that other citizens be denied the opportunity for judicial resolution of disagreements which are generally less significant than deprivation of personal liberty. The issue of unnecessary delays in the court system must be addressed in this as well as in other spheres, but it cannot be solved by substituting a system that provides for abandonment of such proceedings and safeguards.

The central issue is that the deprivation of personal liberty either by involuntary hospitalization or by involuntary treatment is a major occurrence. All persons who are faced with the temporary or permanent loss of these most basic rights of citizenship should be entitled to a hearing before an impartial judge, not a committee of colleagues of those seeking to deprive them of these liberties. We know that circumstances do exist when such drastic action is necessary and we can provide our expert testimony to the court, but it is not our role as physicians to make judgments affecting basic civil rights.

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## Dr. Zito and Associates Reply

SIR: We appreciate Dr. Greer's interest in patients' right to refuse treatment. It appears that his experience in Rhode Island is different from that in New York. Anecdotal reports of withdrawn applications, in our experience, have been related to the agreement by patients to take medication and not to anticipation by the treatment team of a judgment against involuntary treatment. Our view is consistent with that of Dr. Lisa Callahan, which we cited in an earlier article (1). In her evaluation of treatment refusal by Ohio forensic patients, she reported that among the 36% of applications that were withdrawn, many involved patients who had decided to take medication because they were pessimistic about the outcome of court review. Overall, our experience does not support the inference of Dr. Greer's statement that "nearly one-half of applications do not result in orders for involuntary treatment," because the one-third of applications that are withdrawn mainly represent agreement by patients to be medicated.

The second point raised in the letter indicates a misreading of our basic position. We fully advocate access to court review of drug refusal for individuals (whether treatment team or patients) who fail to be satisfied by clinical review.

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## Involuntary Interventions: Does the Benefit Exceed the Cost?

SIR: I was pleased to see two provocative articles in the April 1991 issue that began to evaluate critically the costs and benefits of involuntary interventions with patients.

Fred S. Berlin, M.D., Ph.D., and colleagues (1) called into question the mandatory reporting of suspected sexual abuse of children. In their sexual disorders clinic, this policy has ended the flow of such information from adult patients to their clinicians and has diminished the number of adult patients seeking voluntary treatment. The net result may be that children are actually less protected by a well-intentioned policy which invades and strains the doctor-patient relationship. The study was severely limited because it only looked at a sexual disorders clinic, but it was provocative nonetheless.

Francine Cournos, M.D., and colleagues (2) examined the long-term outcome of involuntary antipsychotic medication among state hospital patients. Their data demonstrate that the outcome for patients who are involuntarily medicated by court order is essentially the same as for those voluntarily taking medication. The authors concluded that these results argue against the substantial effectiveness of involuntary medication. One could equally well argue that outcomes similar to those of voluntarily medicated patients support the utility of this intervention. However, this comparison is not the vital one. What we as clinicians would really like to know is whether the involuntarily medicated do better than medication refusers who are not coerced. Other than medication given involuntarily to protect patients and others from acute danger, which is clearly clinically mandatory, are we accomplishing anything by medicating patients against their will? Is this violation of individual rights and perturbation of the doctor-patient relationship—so costly in professional time and energy as well—worth it? Unfortunately, Dr. Cournos and associates' study, unlike that of Dr. Berlin and colleagues, is a tease. I look forward to publication of a set of data that give me some useful insight into this critical issue.

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CHARLES E. SCHWARTZ, M.D.
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## Dr. Berlin and Associates Reply

SIR: We agree with Dr. Schwartz that our data support the conclusion that mandatory reporting of suspected child sexual abuse may sometimes result in children being less well, rather than better, protected. We also agree that our data documented a decreased flow of important clinical information from patients to physicians—information that possibly could have led to early preventive intervention.

Others apparently share our concerns. Some clinical researchers operate under a federal Certificate of Confidentiality. This certificate supersedes state mandatory reporting statutes. It is used because of the recognition that accurate and relevant data cannot be obtained unless patients feel free to communicate openly and honestly.

In a recent survey of 1,196 mandated reporters in 15 states, almost 40% of those polled admitted that they sometimes failed to report suspected child abuse or neglect (1, 2). Those surveyed included general and family practitioners, pediatricians, psychiatrists, clinical psychologists, social workers, school principals, and heads of child care centers. Finkelhor and Zellman (3) documented that much of the noncompliance with reporting requirements was the result of "reasoned decisions by well trained and committed child abuse professionals." According to these researchers, otherwise compliant reporters knowingly and purposely violated the law in cases where they believed that a report would compromise a given child's best interests. We appreciate the possible motives but disagree with this practice. It would be better to try to have the relevant laws changed.

We believe that important legislative decisions which affect the physician-patient relationship should be based on objective evidence regarding what is best for patients and/or society rather than on what is politically popular or "politically correct." Our article attempted to present objective data in the hope that this would be helpful.

We believe that the psychiatric profession itself, as well as legislators, should strive for professional objectivity. The diagnostic category of "paraphilic coercive disorder" was omitted from *DSM-III-R* in large part because of political pressure from feminist groups who believed that the existence of a psychiatric disorder which might predispose some men to rape was troublesome and unacceptable. The decision to exclude that diagnosis was made by the Board of Trustees of APA in spite of a consensus by members of the subcommittee on the paraphilias that there were sufficient scientific data to support its inclusion. Paraphilic coercive disorder is a psychiatric condition in which afflicted individuals recurrently experience intense eroticized fantasies and urges about coercing others into sexual activity.

Dr. Schwartz's letter addresses the issue of involuntarily medicating psychiatric patients. We again agree that relevant evidence needs to come from objective studies—in this case, from studies showing that involuntarily medicated patients do better than medication refusers. We are not convinced, however, that involuntary administration of medication involves the same sort of potential conflict of interest between patient and physician as does mandatory reporting. Understandably, mandatory reporting statutes are not based on a concern about what is best for the reported patient. On the other hand, the purpose of involuntary medication is often to restore mental functions, such as impaired reasoning, in the belief that a given patient, once restored to a rational state, will be better off and perhaps even appreciative. Safeguards against abuse of involuntarily administered medications are, of course, crucial.

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## Dr. Cournos and Associates Reply

SIR: We appreciate Dr. Schwartz's interest in our study on the outcome of involuntary medication and his sensitivity as a clinician. His letter expresses important concerns about how involuntary medication affects the doctor-patient relationship.

Psychiatrists are undoubtedly reluctant to strain the doctor-patient relationship by using coercion to get patients to take medication. This probably explains why involuntary medication appeared to be a last resort in the settings we studied and was formally petitioned for only 0.37% of patients in New York City's adult state hospitals during the study period. As part of the involuntary treatment decision-making process, the psychiatrist is required to explain available treatments, including their risks and benefits, and assess the patient's capacity to reach a treatment decision (1). In this process, it is likely that the patient and the psychiatrist will achieve a better understanding of each other and that patients who are less ill can either be persuaded to accept medication or be discharged without it (2). The most desirable long-term outcome is, of course, that the patient will continue appropriate treatment without coercion (3).

Dr. Schwartz would like to know whether, among nondangerous patients who refuse medication, those who are involuntarily medicated do better than medication refusers who are not coerced. This question is very difficult to study. Only six of the 51 involuntarily medicated patients in our sample did not present a significant danger to themselves or others. In practice, dangerousness is probably the principal criterion used by clinicians for deciding to pursue formal involuntary medication. For obvious ethical reasons, it is not possible to use random assignment to decide which cases to pursue.

Nevertheless, we feel that our study answered some of Dr. Schwartz's questions about the substantial effectiveness of involuntary medication. Involuntary medication appeared to be an essential short-term management strategy for most of our subjects. Treating psychiatrists reported improvement of symptoms in a majority of involuntarily medicated patients. Almost all patients in our study were being treated under duress, since, whether they took medication voluntarily or by coercion, 90% were in the hospital on an involuntary status. Both groups demonstrated long-term limitations in efficacy of and compliance with medication. We feel that our article presented a useful insight into these long-term limitations, and we hope it will contribute to the development of more informed and effective approaches to treatment refusal.

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## Outcome of Schizophrenia

SIR: Although it was primarily concerned with the course of schizophrenia, the recent excellent study by Joanne Marengo, Ph.D., and associates (1) presented some unemphasized features of interest. The authors' data contradict Kraepelin's view that schizophrenia inevitably has a chronic, deteriorating course and, in fact, actually support an upbeat view of the course and outcome of the schizophrenias.

The authors' "glass-half-empty" view of the outcome of schizophrenia was expressed by the statement that "approximately one-fifth of the group showed recovered or mild outcomes, one-fifth showed very severe impairment, and the remaining three-fifths showed intermediate outcomes" (p. 609).

A "glass-half-full" view of the data can be generated when the recovered and mild outcome groups in the authors' study and those of Ciompi and of Bleuler are combined: 51.4%, 48.7%, and 51.9%, respectively (Dr. Marengo and associates' table 3). An equally upbeat interpretation has been made by Bleuler (2), Ciompi (3), and Harding et al. (4), who rightly emphasize the "wellness" potential inherent in schizophrenic disorders and urge therapists to eschew despair in treating these individuals. As Harding et al. put it, "Systems of treatment are not as yet able to cure, but they should be able to remove the obstacles that stand in the way of natural self-healing processes" (5, p. 483).

The widespread "glass-half-empty" view of schizophrenic disorders probably originates in the fact that the contact of mental health workers with schizophrenia has almost exclusively involved the 40%–50% of patients with schizophrenia who do poorly (i.e., the moderately severe and very severe outcome groups in the studies by Dr. Marengo and associates, Ciompi, and Bleuler). The fact that certain schizophrenic subgroups, presently not recognizable a priori, have the potential for a good outcome has profound implications for research and treatment strategies. Objective definitions of these subtypes would facilitate their early recognition. Identification of "wellness" factors, not inherent in the nuclear schizophrenic process but profoundly influencing its course and outcome, is also obviously desirable.

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## Dr. Marengo and Associates Reply

SIR: We thank Dr. Kopelowicz and Dr. Bidder for addressing some important issues relevant to this area of research. Actually, the intended phrase should have correctly read, "Approximately one-fifth of this group showed recovered outcomes, one-fifth showed very severe impairment, and the remaining three-fifths showed intermediate outcomes." This does not alter the issues that Dr. Kopelowicz and Dr. Bidder raise, issues with which we struggle as well.

Whether one wishes to combine recovered and mild outcomes in a conceptualization that promotes an upbeat view or one wishes to conceptualize mild outcome as lying within an intermediate range may be decided differently depending on the context of discussion or the meaning of such groupings for the interpreter. Our presentation of the criteria used for all outcome categories allows readers to grapple with such issues themselves.

Patients with a mild end state experience psychopathology and differ from patients experiencing recovery. To reiterate, a mild end state, as defined in Manfred Bleuler's 1978 study (1) (and therefore also in our and Ciompi's [2, 3] comparative investigations), is entered by patients who can maintain a sensible conversation, at least about topics that do not concern their delusional or hallucinatory experiences. Overt behavior is generally normal, and the illness is not immediately obvious if one becomes involved in conversations. These patients perform useful work. Bleuler noted that definite schizophrenic symptoms do exist in these patients, that they can live either outside the institution or on quiet wards, and that the group includes patients whose delusional or hallucinatory ideas lie near the surface, although deterioration of personality is not in evidence. Since we did not have any older adult patients in our patient group (a group that was, on average, 31 years old at the 10-year assessment point of our study), we did not use Bleuler's final inclusion criterion; that is, the mild outcome group may include "some aged eccentrics who have rejected life, who scarcely manifest any normal interests, are incapable of performing even simple mechanical tasks, or who pursue any sort of whimsical idea" (1, p. 191).

Regarding what Dr. Kopelowicz and Dr. Bidder feel is an underemphasis of the outcome results, we had hoped that our "course" approach would bring an additional perspective to the data that exist on outcome alone. Illness onset, the course of symptoms (i.e., episodic or chronic), and outcome were given equal weight in defining and discussing syndrome courses.

Finally, with regard to the significant issue of identifying subgroups of individuals with schizophrenia who may be targeted for specific research or treatment strategies, we too supported this goal in the Discussion section of our article. Along with other longitudinal investigators, we propose that information on onset and course as well as outcome may serve to improve the definition of such subgroups. As additional or longer-term studies accumulate, we hope to be in an even better position to consider the full range of possibilities for treatment and prognoses in schizophrenia.

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### Borderline Patients' Perceptions of Their Parents

SIR: Hallie Zweig-Frank, Ph.D., and Joel Paris, M.D. (1) reported that patients with borderline personality disorder perceive their parents as having been less caring and more overprotective than do nonborderline patients. Although the authors appropriately included a number of cautions regarding extrapolation from their findings, they suggested that the results support the etiologic theory of Masterson and Rinsley (2).

The differences between borderline and nonborderline patients were statistically significant, but were they meaningful? The average difference in ratings between the two groups of patients was less than one-half of a standard deviation. Thus, the great majority of the borderline patients' ratings of parental care and protectiveness fell well within the comparison group's range and, apparently, the reported "normal" range as well. This small effect size cannot provide any substantial support for a developmental theory which suggests that parental interactions with the child, particularly between the ages of 18 and 36 months, are vital to the development of borderline personality disorder.

As Dr. Zweig-Frank and Dr. Paris noted, borderline personality disorder is likely to be of heterogeneous origin. For some individuals, parental behaviors, particularly extreme behaviors such as physical and sexual abuse, may be major contributing factors. For other individuals, the causation may be reversed. A child who is intrinsically difficult to comfort may correctly (or incorrectly) perceive less comfort. A child with attention problems or impulsive behavior may evoke more protective parental behavior. Finally, for some individuals, there will be no evidence of abuse, neglect, and overprotectiveness. Theories of borderline personality disorder must encompass this apparent etiologic heterogeneity.

We applaud the quantitative design used by Dr. Zweig-Frank and Dr. Paris but would emphasize that the available retrospective data about the family environment and early experiences of individuals with borderline personality disorder are not particularly consistent across studies and do not shed much light on the validity of various conflicting developmental theories of the etiology of the disorder. We might add even more emphatic cautions about the limitations of existing data regarding possible biological underpinnings for borderline personality disorder. It seems most likely that the disorder arises from complex interactions between biological predisposition and experience.

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### Dr. Paris and Dr. Zweig-Frank Reply

SIR: We appreciate the thoughtful letter from Dr. Cowdry and Ms. O'Leary, which also gives us the opportunity to clarify some points raised in our article. We agree that the etiology of borderline personality disorder is complex and that there is most likely a biological predisposition involved. We also agree that no single factor can account for the etiology of the disorder; we are, in fact, in the midst of a large-scale study of a number of risk factors for borderline personality disorder. We therefore look forward to contributing to a multidimensional framework, as proposed by Dr. Cowdry and Ms. O'Leary.

We did not claim that our findings were specific to borderline personality disorder, but only that they were more common in this group of patients than in comparison groups. As the letter correctly points out, there was important overlap in the scores of borderline and nonborderline patients. We wish to make clear that in quoting Masterson and Rinsley, we did not intend to support all of their ideas. Our point was that this was the first time that there was any empirical evidence, however partial or indirect, to support their position. In fact, our findings of combined neglect and overprotection are not consistent with Masterson and Rinsley's hypothesis of simple maternal overinvolvement. Moreover, our research does not suggest that such overinvolvement is limited to any particular developmental stage. Our instrument, the Parental Bonding Index, is designed to measure recollections of abnormal parenting over the first 36 years of life. Our borderline group reported that their parents interfered with their autonomy all through their childhoods.

We do not agree with Dr. Cowdry and Ms. O'Leary that findings across studies have been inconsistent. We feel that our hypothesis of biparental failure accounts for most of the evidence. However, we do not believe that childhood experiences alone can account for the psychopathology of borderline personality disorder.

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### Change in Ideational Content as a Prodromal Symptom in Affective Disorders

SIR: "Prodromal Symptoms in Affective Disorders" by Giovanni A. Fava, M.D., and Robert Kellner, M.D., Ph.D. (1) is an important contribution. The concept itself is significant. The illustrative material clearly demonstrates that prodromal symptoms do occur with notable frequency.

For two decades—a generation—American psychiatry has been going through the laborious process of defining the area of our work. That enormous effort, which produced the *Di-*

*agnostic and Statistical Manuals,* has been remarkably successful, not only in this country but around the world. It is now time to go further, to explore more deeply into the nature of these now operationally well-defined entities we call disorders. Dr. Fava and Dr. Kellner did that. They opened a door to a developmental, longitudinal understanding of the disorders, which so far have been defined by cross-section.

There is one omission from the list of prodromal symptoms described. I could not find any reference to ideational content, i.e., to preoccupations, thoughts, and ideas. In my paper "Transitional and Pre-psychotic Symptoms in Depression" (2) I described cases in which depressions were preceded by spontaneous memories of traumatic situations of childhood, either as overt memories or as dreams, occurring several weeks before the onset of the depression. These experiences had a strikingly vivid sensory quality and felt "forced" on the patient. For example, one woman kept seeing the hallway of her father's house, in which his casket had stood, as she had seen it years before. She could not get it out of her consciousness. Another woman who had not had a depression for several years came into therapy because she had had a dream "of when we were children and lived behind the store. All the things I could not change."

Some of these experiences resemble "flashbacks" of the kind seen in marijuana smokers. They also resemble the induced hallucinatory experiences described by Penfield (3), elicited by electrical stimulation of the temporal lobe. This kind of "return of the repressed" is much more sudden than the gradual recovery of memories during psychoanalysis. These observations were made with long-term patients, for whom the onset, the course, the recovery, and the aftermath could be followed. I doubt that they would have been elicited by any statistically oriented paper test. My conclusion was that depression is a longitudinal process that goes through stages. Sensory illusions, repetitive dreams of death, and memories of childhood trauma occur at a time when a more advanced stage of depression threatens to develop.

As for mania, Loeb and Loeb (4) described cases in which an oncoming manic episode was heralded by a marked increase in conscious and unconscious sexual thoughts, feelings, and behavior before any observed deterioration in ego or superego functioning.

Thus, there is evidence that changes in ideational content should be included in the list of prodromal symptoms of affective disorders.

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## Dr. Fava and Dr. Kellner Reply

Sɪʀ: We are grateful to Dr. Badal for his comments. In our review we did not deal with ideational content, preoccupations, thought, and ideas as prodromal symptoms. We limited ourselves to published empirical studies of prodromal symptoms, and in our search we had found no reference to such studies of these phenomena. We have observed in our clinical work with some patients that intrusive ideas and images, which Dr. Badal describes, preceded an episode of melancholia or an endogenous depression. We have also observed thoughts as well as behaviors that were uncharacteristic for the patient which preceded the onset of mania, as described by Loeb and Loeb. We agree with Dr. Badal that these phenomena are important, they should be included in a list of prodromal symptoms, and they should be a topic for further systematic research.

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## Information Theory Perspective on the Mind-Body Problem

Sɪʀ: In his article on the mind-body problem, Aviel Goodman, M.D. (1) presented an interesting merger of biopsychosocial systems theory and mental-physical identity theory. Identity theory asserts that mental and physical events are identical but are experienced as different forms of knowledge, because the physical is intersubjectively confirmable, whereas the mental is only subjectively confirmable. I believe that this argument of identity theory is erroneous. There are substantial reasons for believing that something exists which is differentiable from the physical.

The physical (matter and energy) has measurable properties such as mass, volume, and frequency. Measurement has an objective nature, since it is a quantitative process and quantities are the same, within limits, to any observer in the same frame of reference. Transforming the physical changes it into something else.

In order to analyze the mental in a similar fashion, I agree with MacKay (2) that considering the problem from an information-processing point of view is most useful. The following arguments can then be made.

1. Information must also exist. Information can reproducibly generate activity, such as a computer magnetic tape directing a machine or the will directing the body. It is the information contained in an encoded message that controls activity, rather than a direct mechanical process.

2. Information exists in a form of the physical, but it is differentiable from the physical. a) Information is communicable, not measurable. The essence of information is the meaning contained in a physical representation. We can measure the letter "I" or the sound "I" but we cannot measure what it means. Representations become understood through a process of information exchange, i.e., communication. b) Information is transformable. It is essentially the same no matter what physical form it is in so long as the meaning is retained. "I" means myself whether it is spoken or written. c) Information is subjective and qualitative, not objective and quantitative. It is meaningless without an observer who understands it. Understanding is a subjective quality that depends upon and varies with the individual observer.

3. Since one aspect of mind is that it is the information in an information processor—the brain—the meaningful mind is differentiable from the physical brain. The mental is dominant over the physical in the sense that information can direct

activity. Causality is not violated, since information exists in a physical form.

In the information-processing view, then, mental events correspond directly with physical events in the brain, but they are not identical. The physical events are objectively measurable. The information related to those events exists in its own right but is only known subjectively unless it is communicated to others. A neurophysiologist can make an infinite variety of measurements but will not be able to associate those measurements with the thoughts that occurred when the measurements were made unless he or she asks what they were. This supports the psychotherapeutic method of asking patients what things mean to them, for that is the only way we will find out.

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ANDREW J. HERITCH, M.D.
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## Dr. Goodman Replies

SIR: In his letter Dr. Heritch presents an information theory perspective on the mind-body problem, which he contends is incompatible with mental-physical identity. I appreciate the value of the information theory and the insights it entails, and I see it as entirely compatible with mental-physical identity. Information theory represents a mode of knowing events and processes in the realm of mental concepts, much as theories that pertain to objective measurement represent a mode of knowing events and processes in the realm of physical concepts. It is precisely because these modes of knowing are different that mental-physical identity theory is so important, as a framework for understanding the relation between informational and objective knowledge.

Dr. Heritch's main point against mental-physical identity is that "something exists which is differentiable from the physical." Identity theory concurs that mental is differentiable from physical: they are different classes of concepts that are associated with different ways of experiencing and knowing. The identity specified by the theory is identity of reference or extension: the referent of every mental concept is identical with the referent of some physical concept. Identity theory does not state that mental and physical concepts are identical, and intensional identity is specifically excluded, as I discussed in my article (p. 556).

Perhaps Dr. Heritch's argument is asserting not merely that mental and physical concepts are differentiable but that there exist mental entities and events that are differentiable from physical entities and events. In that case, he would be arguing against mental-physical identity by advocating dualism. The philosophical and scientific arguments against dualism are many, and to reiterate them would exceed the scope of this communication. The following brief sample is reproduced from my article (p. 555).

> Perhaps the most decisive argument is that dualism fails to account adequately for the causal relationship between mind and brain, as first argued by Kant; how could a mind with no spatial existence or extension influence a physical brain extended in space? More recently, Fodor . . . wondered how a nonphysical mind can give rise to physical changes without violating the laws of conservation of mass, energy, and momentum. Furthermore, if a mental force that could influence physical entities and processes were postulated, it would then by definition also be a physical force, which would not be consistent with dualism.

Other than this question of differentiability, on which I may or may not agree with Dr. Heritch (depending on whether he is advocating dualism), the only other points with which I might take issue are those in the paragraph preceded by the numeral 3. I am willing to consider the hypothesis that the physical term which shares the referent of the mental term "human mind" is "human brain," although I believe that arguments could be made in favor of hypotheses of correspondence that relate other physical terms with "human mind"—for example, "human organism" or even transpersonal terms like "human society" (I touched upon this issue on p. 559 of my article). I would, however, dispute the locution that describes information as being "in" the brain, on grounds related both to mental-physical identity theory and to information theory. From the standpoint of identity theory, mental terms like "information processing" can be said to correspond with (have the same referent as) physical terms describing neurophysiological processes that occur in the brain; but to say that information itself is in the brain reflects a confusion of logical categories. And, according to (at least some versions of) information theory, information is not a thing but an aspect of the relationship between a potentially meaningful sign and an active interpreter (i.e., interpreting system). It is thus not located "in" either the sign or the interpreter but is a property of the system that they together comprise. I would also dispute the notion that "the mental is dominant over the physical," since 1) it presupposes dualism and 2) it would be questionable even if dualism were valid (for example, it does not seem to be consistent with the fact that psychoactive drugs, even those administered against one's will, have predictable mental effects). Finally, I am not sure how the statement "information exists in a physical form" could be meaningfully interpreted except in the context of mental-physical identity theory.

I thank Dr. Heritch for his interest and for stimulating my own interest in integrating mental-physical identity theory with information theory.

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## Comments on the Proposal to Eliminate the Organic Mental Disorders Category in *DSM-IV*

SIR: A recent letter to the Editor commented on a crucial development in diagnostic psychiatry. Robert L. Spitzer, M.D., and associates (1) supported the proposal to eliminate the category of organic metal disorders from *DSM-IV*, replacing the term "organic" with other terms such as "cognitive impairment disorders" and "secondary" syndromes. Organic mood disorders, for instance, would become secondary mood disorders. Z.J. Lipowski, M.D. (2) provided valid general arguments for retaining the rubric of organic mental disorders in *DSM-IV*. I would like to add some specific comments on depression and challenge the idea that the term "secondary" is more precise and appropriate, as Dr. Spitzer and associates suggested.

There is a considerable body of knowledge, reviewed in detail elsewhere (3, 4), suggesting the occurrence of "organic mood syndromes" or "symptomatic depressions" in which a specific organic factor, on the basis of brain pathology or neurotransmitter balance, is judged to be etiologically related to the mood disturbance, and the organic factor is part of an illness or is a drug (not just any illness or drug) for which there is evidence in the literature that there is resolution of the mood disorder upon specific treatment of the medical disease or discontinuation of the drug. Such diagnosis entails important clinical implications (e.g., often, poor response to antidepressants) that warrant separation from other mood disorders. The primary-secondary differentiation is mainly based on Robins and Guze's distinction (5) between primary depression (affective illness that is not part of another psychiatric or physical disorder) and secondary depression (a mood disorder chronologically superimposed on a nonaffective disturbance). Its reliance on chronology may be appropriate when depression is secondary to another psychiatric disorder, but it may be misleading in the medically ill, when depression may be one of the earliest manifestations of medical illness (3, 4).

For instance, 40% of patients with Cushing's syndrome reported a major depressive disorder either immediately before or at the onset of illness (6). Should those cases be classified as "primary depressions"? The likelihood of recovery after successful correction of hypercortisolism (3, 4) makes this categorization questionable, if not misleading. In Cushing's disease, depression and hypercortisolism may be two distinct yet ostensibly related manifestations of suprapituitary disease (6). Setting a primary-secondary hierarchy would be arbitrary and not in keeping with current understanding of the complex interaction of neurophysiological, biochemical, and behavioral factors in medical disease. The definition of organic mood disorder in *DSM-IV* can be improved—for instance, by setting the intensity threshold of a major depressive disorder and adding a tentative list of medical diseases and drugs known to cause it (4)—and should not be replaced by a term ("secondary") that is likely to generate confusion.

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## Dr. Spitzer and Dr. First Reply

SIR: We appreciate Dr. Fava's comments on our suggestion to remove the term "organic mental disorders" from *DSM-IV*. We are in complete agreement with Dr. Fava about the importance of distinguishing cases of mood disturbance that are judged to be etiologically related to a known physical illness or drug from cases without such a relationship. We recognize the potential confusion with our suggested term, "secondary mood disorder" to mood disturbances that are judged to be due to a physical illness. As Dr. Fava points out, this term was used by Robins and Guze to refer to mood disturbances that temporally followed a nonaffective illness. Our use of the proposed term does not depend on the temporal relationship but is entirely an etiological judgment, as it now is in *DSM-III-R* for "organic mood disorder." Although in most cases the mood disturbance of a secondary mood disorder would follow the appearance of the symptoms of the physical illness, Dr. Fava correctly notes that this is not always so.

As we have noted elsewhere (1), Robins and Guze's use of the term "secondary" was only a research strategy for maximizing homogeneity of research subjects in studies of affective disorders. We therefore expect that for researchers and in general clinical settings, there will be little confusion with our recommended use of the term.

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1. Spitzer RL, First MB, Williams JBW, Kendler K, Pincus HA, Tucker G: Now is the time to retire the term "organic mental disorders." Am J Psychiatry 1992; 149:240–244

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## Update of Review of Guides for Patients

SIR: We appreciate the review by Brian L. Cook, D.O., of several of our guides for patients (1). Since we pride ourselves on the timeliness of our publications, we want readers to know that the guides are regularly revised. To update Dr. Cook's review, *Carbamazepine and Manic-Depression: A Guide* was revised in 1990, and *Obsessive Compulsive Disorder: A Guide* was revised in 1991 (in part to incorporate the availability of clomipramine).

We should also like to correct the prices that were listed in the review. The cost per booklet is $3.95 (which includes postage and handling), with reduced rates for orders of 10 or more.

REFERENCE

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## Prescription Writing

SIR: In his response to the presidential address (1), Lawrence Hartmann, M.D., the President-Elect of APA, offered his position on psychologists with the slogan "No medication without medical education." However, the horse left the barn a long time ago. Psychologists, social workers, pastoral counselors, drug therapists, etc. are already prescribing medication.

For over 10 years, I worked at community mental health centers and other government clinics. Social workers, psychologists, and nurses do the diagnosis and treatment. When they decide that a patient needs medication, they schedule the patient for the "medication clinic." At intervals—perhaps twice a week, once a week, or once a month—a psychiatrist is brought in to sign prescriptions for an unlimited number of patients. Instead of seeing patients individually in the traditional doctor-patient relationship, the psychiatrist frequently sits on a committee as a member of the "treatment team." The only resemblance to standard protocol as taught in medical schools is that the psychiatrist holds the pen.

I believe that psychologists and social workers should sign their own prescriptions, so the public will then be aware of whose cognitive efforts are responsible for a particular prescription. When this century opened, asylums were filled with cases of general paresis of the insane. A little effort should close the century the same way, with nonphysicians feeding antidepressants and antipsychotics to syphilitic patients.

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### Dr. Hartmann Replies

SIR: Horses have been leaving barns in various ways for centuries, but many of them have returned. Even I, mostly a city dweller, have ridden a good many horses back into barns. Is Dr. Nelson suggesting that any horse that leaves a barn should be given up for lost? Is that a Texan custom? Is that a local interpretation of (if you will forgive a play on words) a hippocratic oath?

I do not fully understand Dr. Nelson's letter, but my "No medication without medical education" seems to me a minimal sensible slogan to protect patients. I hope and assume he is being ironic when he suggests that in the 1990s social workers should medicate patients with syphilis.

Certainly, there are pressures on many of us in hospitals, health maintenance organizations, community mental health centers, and elsewhere to write prescriptions for patients we do not adequately know or have not even seen. But psychiatrists, all of us, have an ethical obligation to resist such pressures. Ethics and good patient care command us not to write prescriptions for patients we have not seen and/or do not adequately know. Courage may be needed—and tenacity, patience, and support from colleagues—and it is often difficult; but I do not think it takes a particularly unusual grasp of humane values and biopsychosocial integration to be aware of medical and psychiatric ethics and, as individuals and as a profession, to resist pressures against our ethics.

Some horses should sometimes be ridden back into barns.

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*Reprints of letters to the Editor are not available.*

### Correction

In the article "Magnetic Resonance Spectroscopy in Psychiatry: Potential, Pitfalls, and Promise" by M.S. Keshavan, M.D., et al. (August 1991 issue, pp. 976–985), the term "phosphocreatinine" should be read as "phosphocreatine" throughout.

## *APA Official Actions*

# The American Board of Psychiatry and Neurology, Inc.: Report on the 1991 Examinations

*The following successfully completed the Board examination in January 1991.*

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*Special Articles*

# Depression and Parkinson's Disease: A Review

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*Objective: The purpose of this review is to provide an update of the research regarding depression in Parkinson's disease and to synthesize the information into a neurobiological model relating the structural and biochemical changes in this disorder to the behavioral manifestations. Method: The author used a computer-based search of the literature, augmented by extensive bibliography-guided article reviews, to find information on depression and Parkinson's disease. Findings: Depression occurs in approximately 40% of patients with Parkinson's disease; depression in Parkinson's disease is distinguished from other depressive disorders by greater anxiety and less self-punitive ideation. Lower CSF levels of 5-hydroxyindoleacetic acid, a past history of depression, and greater functional disability are associated with a greater risk of depression in Parkinson's disease. Female gender, early age at onset of Parkinson's disease, and greater left brain involvement may also be risk factors. Approximately half of depressed patients with Parkinson's disease meet criteria for major depressive episodes; half have dysthymia. Depression is more common in Parkinson's disease with prominent bradykinesia and gait instability than in tremor-dominant syndromes. Depressed patients with Parkinson's disease have greater frontal lobe dysfunction and greater involvement of dopaminergic and noradrenergic systems than nondepressed patients with the disease. Mood changes in Parkinson's disease respond to treatment with conventional tricyclic antidepressants or ECT. Conclusions: Neurobiological investigations suggest that depression in Parkinson's disease may be mediated by dysfunction in mesocortical/prefrontal reward, motivational, and stress-response systems. Neuropsychological, metabolic, clinical, pharmacological, and anatomical studies support the involvement of frontal dopaminergic projections in patients with Parkinson's disease and depression.*

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Dramatic strides have been made recently in understanding the pathophysiology and treatment of Parkinson's disease. In addition to the well-established success of dopaminergic therapy, administration of selegiline, a monoamine oxidase B (MAO-B) inhibitor, may intervene in the degenerative process (1), and transplantation of fetal tissue into the basal ganglia may permanently ameliorate the motor disability (2). Despite these advances, many aspects of Parkinson's disease remain poorly understood, particularly its behavioral manifestations. Depression is the most common neuropsychiatric disturbance of Parkinson's disease, but its frequency, characteristics, course, treatment responsiveness, and neurobiological substrates are at best only partially established. In this review, the literature regarding mood changes in Parkinson's disease is examined, the relationship of depression to the neuropathology and neurochemistry of Parkinson's disease is dis-

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**TABLE 1. Reported Rates of Depression in Parkinson's Disease**

| Study | Year | Number of Subjects | % Depressed | Assessment Method |
|---|---|---|---|---|
| Patrick and Levy (3) | 1922 | 146 | 7 | Clinical diagnosis |
| Mjones (4) | 1949 | 238 | 40 | Clinical diagnosis |
| Strang (5) | 1965 | 30 | 67 | Clinical diagnosis |
| Hoehn and Yahr (6) | 1967 | 802 | 4 | Clinical diagnosis |
| Warburton (7) | 1967 | 140 | 59 | Clinical diagnosis with operationalized severity rating |
| Celesia and Wanamaker (8) | 1972 | 153 | 37 | Clinical diagnosis with severity rating |
| Brown and Wilson (9) | 1972 | 27 | 52 | Chart review guided by rating scale |
| Mindham et al. (10) | 1976 | 50 | 50 | Chart review with defined psychiatric diagnoses |
| Lesser et al. (11) | 1979 | 131 | 32 | Clinical diagnosis |
| Lieberman et al. (12) | 1979 | 520 | 29 | Clinical diagnosis |
| Presthus (13) | 1980 | 175 | 12 | Clinical diagnosis |
| Mayeux et al. (14) | 1981 | 55 | 47 | Rating scale |
| Gotham et al. (15) | 1986 | 187 | 69 | Rating scale |
| Santamaria et al. (16) | 1986 | 34 | 32 | *DSM-III* diagnosis and rating scale |
| Mayeux et al. (17) | 1986 | 49 | 43 | Structured interview and *DSM-III* diagnosis |
| Oyebode et al. (18) | 1986 | 43 | 21 | Clinical diagnosis |
| Taylor et al. (19) | 1986 | 30 | 70 | Rating scale |
| Kostic et al. (20) | 1987 | 26 | 54 | Rating scale |
| Huber et al. (21) | 1988 | 60 | 32 | Rating scale and *DSM-III* diagnosis |
| Brown et al. (22)[a] | 1988 | 132 | 27 | Rating scale |
| Darkins et al. (23) | 1988 | 30 | 30 | Rating scale |
| Bieliauskas and Glantz (24) | 1989 | 33 | 70 | Rating scales |
| Sano et al. (25) | 1989 | | | |
| Retrospective | | 339 | 56 | *DSM-III* diagnosis |
| Prospective | | 110 | 30 | Structured interview and *DSM-III* diagnosis |
| Starkstein et al. (26) | 1990 | 105 | 40 | Structured interview and *DSM-III* diagnosis |
| Brown and MacCarthy (27) | 1990 | 40 | 25 | Structured interview |

[a] Follow-up of the study of Gotham et al. (15), involving many of the same patients.

cussed, and a potential integrative psychobiological model is proposed.

## REVIEW METHOD

A computerized search of MEDLINE, the online computer database of the National Library of Medicine, was conducted to identify articles pertaining to depression in Parkinson's disease. A key-word search was made for depression and synonyms of depression, behavior and Parkinson's disease, and psychiatry and Parkinson's disease, as well as tricyclics and ECT in Parkinson's disease. Review articles and individual research articles were consulted and bibliography-guided searches were pursued to augment the computer-based canvas of the literature. Books summarizing symposia on Parkinson's disease were consulted to obtain additional information and to expand the bibliographic pool. The search was limited to articles published in English. Nearly all of the primary research articles specifically addressing depression in Parkinson's disease are referenced in this review.

## DEMOGRAPHIC FEATURES OF DEPRESSION IN PARKINSON'S DISEASE

### *Frequency*

Table 1 summarizes the rates of depression in Parkinson's disease reported in the principal studies addressing this issue (3–27). The mean frequency reported in the 26 studies was 40%; the range was 4%–70%. The lowest reported frequencies were found in studies that were done before standardized rating scales, scripted interviews, or operationalized diagnostic criteria were in general use. Moreover, the dominant theoretical construct in these studies was that depression was a reactive phenomenon; this assumption militated against counting mood changes among the manifestations of Parkinson's disease. The low rates of depression found in some of the early studies can be attributed to these methodological and conceptual contingencies. In the nine studies reported in 1987–1990, the rate of depression ranged from 25% to 70% (mean=43%). Discrepancies in the reported frequencies reflect the use of different definitions of depression, thresholds for identification of a mood disorder, and assessment strategies. None of these studies applied demographic methods with random or comprehensive sampling, and all were subject to patient selection biases. The consistency of the detection of depression across studies supports a relationship between depression and Parkinson's disease, but determination of the true prevalence awaits further study.

Another approach to investigating depression in Parkinson's disease is to administer standardized rating scales and compare the results with known standards for the scale or with simultaneously studied comparison subjects. The Beck Depression Inventory (28) is the instrument most widely used in the quantification of mood changes in Parkinson's disease. Table 2 lists the principal studies of Parkinson's disease in which Beck Depression Inventory scores were reported (14–16, 29–39). With the

**TABLE 2. Reported Beck Depression Inventory Scores of Patients With Parkinson's Disease and Comparison Subjects**

| Study | Year | Mean Score: Patients With Parkinson's Disease | Mean Score: Comparison Subjects | Description of Comparison Subjects |
|---|---|---|---|---|
| Mayeux et al. (14) | 1981 | 11.1 | 6.2 | Spouses |
| Gotham et al. (15) | 1986 | 14.1 | 14.3 | Arthritis patients |
| | | 14.1 | 6.4 | Normal elderly |
| Santamaria et al. (16) | 1986 | 11.9 | 7.0 | Spouses |
| Direnfeld et al. (29) | 1984 | 9.7 | 7.1 | Nonneurological patients |
| Stern et al. (30) | 1984 | 7.9 | 3.8 | Volunteers |
| Freedman and Oscar-Berman (31) | 1986 | 8.5 | 3.8 | Volunteers |
| Levin et al. (32) | 1988 | 11.6 | 6.1 | Spouses and elderly volunteers |
| Huber et al. (33) | 1989 | 8.1 | 4.7 | Spouses |
| Gibb and Lees (34) | 1988 | 13.1 | | |
| Spicer et al. (35) | 1988 | 12.3 | | |
| Huber et al. (36) | 1989 | 9.3 | 5.1 | Spouses |
| Beatty et al. (37) | 1989 | 9.8 | 4.0 | Community members |
| Ehmann et al. (38) | 1990 | 11.0 | 6.7 | Disabled |
| Huber et al. (39) | 1990 | 9.7 | 4.0 | Volunteers and spouses |

exception of a study that used arthritis patients as the comparison subjects (15), the Beck Depression Inventory scores of patients with Parkinson's disease were higher than the scores of comparison subjects. The range of scores for the patients with Parkinson's disease was 7.9–14.1; the range for the comparison subjects (excluding the study that used arthritis patients) was 3.8–7.1. All of these studies were based on clinical populations and were subject to referral and research participation biases.

The Beck Depression Inventory contains items that might be endorsed by patients with Parkinson's disease without depression, confounding motor and mood changes. Levin et al. (32), however, demonstrated with cluster analysis that the potential crossover somatic items clustered with depression rather than with motor elements, suggesting that the Beck Depression Inventory scores are representative of mood changes. Similarly, Starkstein et al. (40) found that potential crossover items accurately reflected the presence of a mood disorder in Parkinson's disease.

### *Current Age, Age at Onset, and Duration of Parkinson's Disease*

A majority of studies have found no relationship between depression and the patient's current age (7, 8, 24, 26, 27, 41) or the patient's age at onset of the Parkinson's disease (7, 15, 33, 34, 42, 43). Santamaria et al. (16) and Starkstein et al. (44), however, found that depressed patients with Parkinson's disease tended to be younger at the time of onset of parkinsonian symptoms. The number of depressed patients in the study by Santamaria et al. (16) was relatively small (N=11), limiting confidence in extrapolating from this study to the general population. The boundary age for early-onset versus late-onset Parkinson's disease has varied among studies, perhaps contributing to the lack of agreement regarding the importance of this variable as a risk factor for depression. Conclusions based on the available data regarding the potential role of age at onset as a contributing factor to the vulnerability to depression would be premature.

The duration of Parkinson's disease might be expected to influence the rate of depression, but most investigators have found no relationship between length of illness and mood changes (7, 8, 15, 24, 27, 38, 41).

### *Gender*

Several studies (7, 8, 15, 27) have found a higher rate of depression among women with Parkinson's disease, but others (9, 38, 39, 41, 45–47) have failed to identify any relationship between gender and mood. Being female may be a risk factor for depression in Parkinson's disease, but a consensus is lacking.

### *Personal and Family History of Depression*

Two studies (14, 26) have identified a past history of depression as a risk factor for a major mood disorder after the onset of parkinsonian symptoms. If confirmed, this observation could be interpreted as demonstrating that individuals vulnerable to depression are more likely to become depressed after onset of parkinsonism or that depression and Parkinson's disease have a linked neurobiology and either may express temporal precedence.

Studies assessing the influence of a family history of psychiatric illness (14, 26) have not found a higher rate of psychiatric illness in the family members of patients with Parkinson's disease or, more specifically, a higher rate of mood disorders in the family members of depressed patients with Parkinson's disease. These reports suggest that, in most patients, depression in Parkinson's disease is unlikely to be a product of an independently inherited familial disorder.

## CHARACTERISTICS OF DEPRESSION IN PARKINSON'S DISEASE

### *Profile of Depressive Features*

Most investigators concur that the profile of depressive symptoms observed in Parkinson's disease is not

**TABLE 3. Reported Rates of Mild and Moderate-to-Severe Depressive Syndromes in Patients With Parkinson's Disease**

| Study | Year | Mild Symptoms (%) | Moderate–Severe Symptoms (%) |
|---|---|---|---|
| Warburton (7) | 1967 | 11 | 81 |
| Celesia and Wanamaker (8) | 1972 | 33 | 67 |
| Mayeux et al. (14) | 1981 | 65 | 35 |
| Gotham et al. (15) | 1986 | 43 | 57 |
| Santamaria et al. (16) | 1986 | 91 | 9 |
| Mayeux et al. (17) | 1986 | 33 | 67 |
| Starkstein et al. (26) | 1990 | 49 | 51 |
| Ehmann et al. (38) | 1989 | 31 | 68 |

identical to that reported in patients with idiopathic depression. Brown et al. (22) analyzed the Beck Depression Inventory scores of 132 patients with Parkinson's disease and found elevated levels of dysphoria and pessimism about the future, irritability, sadness, and suicidal ideation but little guilt, self-blame, or feelings of failure or punishment. This pattern of sadness without guilt or self-reproach has been confirmed by several investigators (19, 32, 39). Other distinctive features of depression in Parkinson's disease include a high rate of anxiety symptoms (15, 48), a relative lack of delusions and hallucinations (27), and a low suicide rate despite a high frequency of suicidal ideation. These observations indicate that depression in Parkinson's disease is subtly different from idiopathic mood disorders and raise the intriguing possibility that there may be disease-specific depression syndromes with distinctive mood profiles in different conditions.

### *Severity and Type of Depression*

Several studies have assessed the intensity of depressive symptoms in Parkinson's disease by using clinical criteria to distinguish between major depressive episodes and dysthymia or by applying rating scales to differentiate mild from moderate-to-severe syndromes. Table 3 summarizes the results of these investigations (7, 8, 14–17, 26, 38). On average, slightly more than half (54%) of depressed patients with Parkinson's disease met criteria for a major depressive episode (moderate-to-severe symptoms) and slightly less than half (45%) had dysthymia or minor depressions (mild symptoms). The proportions varied considerably among studies, again suggesting the influence of considerable selection biases in different study populations. Major and minor syndromes differ in several respects in addition to severity: minor depressions are more likely to remit (49) and are more closely related to disability (26).

### *Course of Depression*

The course of depression in Parkinson's disease has received little study. Brown et al. (22) found that 14 months after preliminary assessment, 11% of depressed patients with Parkinson's disease no longer evidenced mood changes but that an equal percent of patients who had been free of mood changes had developed depressive episodes. Sixteen percent of the entire group of patients were depressed at both assessment periods, and 61% were depressed at neither. Mayeux et al. (49) followed 49 patients with Parkinson's disease for a mean period of 2.5 years; during that time the mood disorders of one of 14 patients with major depression and three of seven patients with dysthymia remitted. No new cases of depression occurred among the 28 nondepressed patients during the follow-up period. These studies suggest that patients with Parkinson's disease may be divided into two groups—one with and one without mood changes—and that the two groups are relatively stable over time.

### *Biological Markers of Depression*

Table 4 summarizes the principal studies of the dexamethasone suppression test (DST) in Parkinson's disease (17, 50–54). The studies indicate that DST results are often abnormal in Parkinson's disease but that the DST lacks adequate sensitivity or specificity to serve as a marker for depression. Thyrotropin-releasing hormone and L-dopa stimulation tests also failed to differentiate between Parkinson's disease patients with and without mood disorders (17).

Studies of CSF 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, have found concentrations to be lower in nondepressed patients with Parkinson's disease than in comparison subjects, and several studies have found lower levels in patients with Parkinson's disease plus major depression than in those without mood changes (17, 20, 45, 49). The severity of depression, however, did not correlate with the 5-HIAA levels, and not all patients with low levels of 5-HIAA were depressed. Substantial differences between CSF 5-HIAA levels of depressed patients with Parkinson's disease were reported by different laboratories (20, 45). These investigations suggest an important role for serotonin in mood alterations but also indicate that the level of CSF 5-HIAA is not by itself an adequate marker for depression in Parkinson's disease.

Neuroimaging studies provide another means of investigating the neurobiology of depression in Parkinson's disease. A recent study using fluorodeoxyglucose positron emission tomography (PET) (55) found that metabolism in the caudate nuclei and orbitofrontal cortex of depressed patients with Parkinson's disease was lower than that of nondepressed patients with Parkinson's disease. The location of the metabolic changes differed from that observed in idiopathic depression, where dorsolateral frontal cortical hypometabolism has been reported (56). The metabolic differences suggest that the pathophysiology of the mood changes may differ in the two disorders. Only a few patients have been studied with PET, and the reproducibility of these results requires demonstration.

Sleep studies have also been used to study the neurobiology of depression in Parkinson's disease. Mean

**TABLE 4. Reported Results of Dexamethasone Suppression Tests in Parkinson's Disease Patients With and Without Depression**

| | | | | Positive DST Results (%) | |
|---|---|---|---|---|---|
| Study | Year | Antiparkinsonian Treatment | Number of Subjects | Parkinson's Disease With Depression | Parkinson's Disease Without Depression |
| Mayeux et al. (17) | 1986 | No | 49 | 75 | 28 |
| Pfeiffer et al. (50) | 1987 | No | 14 | 45 | 17 |
| | | Yes | 32 | 33 | 14 |
| Frochtengarten et al. (51) | 1987 | Yes[a] | 56 | 14[b] | 0 |
| Kuhn et al. (52) | 1989 | No | 35 | 36 | 28 |
| Kostic et al. (53) | 1990 | No | 34 | 75 | 28 |
| Rabey et al. (54) | 1990 | Yes | 32 | —[c] | 47 |

[a] 10 of 56 were untreated.
[b] Depression was defined as Hamilton Rating Scale for Depression score greater than 10.
[c] Depressed patients were excluded from this study.

REM latency has been found to be shorter in depressed than in nondepressed patients with Parkinson's disease, and more depressed than nondepressed patients exhibited shortened REM latency (57). Shortened REM latency is also characteristic of idiopathic depression.

### *Neuropathology*

Neuropathological investigations seeking morphologic correlates of depression in Parkinson's disease are rare and currently inconclusive but point toward changes in noradrenergic and dopaminergic transmitter systems as major contributing factors. Chan-Palay and Asan (58) investigated alterations in the locus ceruleus (the major source of brain norepinephrine) of Parkinson's disease patients with and without depression. The depressed patients had extensive cell loss both rostrally and caudally in the nucleus, whereas patients without depression had relative sparing of caudal neurons. Although the differences between the two groups are provocative, their interpretation is obscure because the caudal cells project to spinal cord and would not be expected to influence mood.

Torack and Morris (59) reported a study of six patients with Parkinson's disease, four of whom were depressed. The common neuropathological correlate of depression was involvement of the ventral tegmental area, hippocampus, and entorhinal cortex. The ventral tegmental area is the source of mesocortical, medial temporal, and orbitofrontal dopaminergic projections, and these cases suggest a role for dopamine loss in depression in Parkinson's disease.

Levels of serotonin in the frontal and temporal poles have been found to be equally low in Parkinson's disease patients with and without depression (decreased by 37% and 47%, respectively) (60).

## RELATIONSHIP OF DEPRESSION TO MOTOR AND COGNITIVE DYSFUNCTION

### *Motor Features*

Several authors have investigated the relationship of mood changes to the classical signs of Parkinson's disease—rigidity, bradykinesia, and tremor—and most investigators (16, 20, 26, 27, 38, 45) have found no association between the mood and motor manifestations of Parkinson's disease. Brown and Wilson (9) observed a modest relationship of depression to rigidity but did not rigorously quantify the association and found no other correlations with the mood disturbance. Huber et al. (21) found that depressed patients with Parkinson's disease exhibited significantly more bradykinesia and tended to have greater rigidity than nondepressed patients, who had more tremor. This observation was supported by the recent multicenter study of selegiline, which found that Parkinson's disease patients with postural instability and gait disturbance evidenced more depression than Parkinson's disease patients with tremor (61). This was a methodologically and analytically sophisticated study, but depressed patients were excluded at entry and the mood changes observed during the course of the research may not be representative of the overall relationship between mood and motor alterations in Parkinson's disease. In general, motor abnormalities do not appear to be major correlates of mood abnormalities, but depression may be more common in syndromes with pronounced gait and postural changes. Among the symptoms of Parkinson's disease, tremor is less responsive to dopamine than are gait changes, akinesia, and rigidity. Thus, depression is most common in syndromes with more prominent dopamine-responsive signs.

### *Disability*

The relationship of depression to disability in Parkinson's disease has been studied with three major approaches: 1) contrasting depression in Parkinson's disease to mood changes in patients with other types of disabilities, 2) correlating depression with severity of impairment of activities of daily living, and 3) studying the relationship of depression to the Hoehn and Yahr staging scale (6).

Several authors compared the frequency of depression in Parkinson's disease with that in other disabled groups. Patients with Parkinson's disease were found to be more depressed than medically ill (7, 47) and paraplegic (41) subjects. Gotham et al. (15), however, compared Parkinson's disease patients with arthritis victims and found that the two groups had similarly elevated Beck Depression Inventory scores. Ehmann et al. (38) overcame many of the methodological flaws of earlier studies and found that patients with Parkinson's disease were significantly more depressed than other disabled patients matched for extent of functional impairment.

In studies of the relationship between depression and severity of functional impairment, a few investigators found no association (7, 16, 46), but most have identified a modest correlation between mood abnormalities and functional deterioration (10, 22, 26, 38).

Finally, the relationship between mood and disability has been investigated by exploring the correlation of depression with the Hoehn and Yahr staging scale (6) (1=unilateral involvement, 2=bilateral involvement without balance difficulties, 3=able to live independently but posture and righting reflexes moderately involved, 4=severe disease but able to walk and stand, 5=confinement to bed or wheelchair). Some investigators found no relationship between Hoehn and Yahr stage and depression (8, 24, 38). Huber et al. (21) reported that depressed patients with Parkinson's disease had a slightly but significantly more advanced stage of disability than nondepressed patients with Parkinson's disease (2.5 versus 1.8). Starkstein et al. (26) noted that patients in stages 1 and 4 had higher depression ratings than patients in the other stages. Thus, there is little agreement about the relationship of mood changes to Hoehn and Yahr staging in Parkinson's disease; no consistent or compelling association between depression and staging is evident.

Analyses of motor symptoms and disability in relation to depression in Parkinson's disease suggest that there is a limited relationship between the severity of disability and the presence of mood changes. The correlation is not sufficiently robust to support disability as a primary determinant of depression in Parkinson's disease. Moreover, these studies do not indicate if the relationship between depression and disability is a product of greater depression in patients with more disability or if depression is another factor increasing the disability of the patient with Parkinson's disease.

### *Lateralized Motor Disturbances*

Parkinsonism may begin unilaterally or may be asymmetrical throughout most of its course. A relationship between depression and lateralized motor changes would imply a role for contralateral structures in the pathophysiology of mood changes. Direnfeld et al. (29) reported that patients with right hemiparkinsonism (greater left brain dysfunction) had somewhat higher Beck Depression Inventory scores than those with a predominance of left-sided signs or those with bilateral involvement (right-sided=13.6, left-sided=7.6, bilateral=9.1), and Starkstein et al. (26) also found that those with more right-sided abnormalities had higher depression rating scale scores. Barber et al. (62), however, found no difference in depression self-ratings between patients with right and left hemiparkinsonism, and Spicer et al. (35) reported a nonsignificant trend toward higher Beck Depression Inventory scores in patients with left hemiparkinsonism (14.1 versus 10.3). Huber et al. (36) found low and approximately equal Beck Depression Inventory scores in patients with right and left hemiparkinsonism (5.2 and 5.8, respectively) and in those with bilateral but asymmetric syndromes (right more severe, 10.5; left more severe, 10.1). At present the evidence concerning a relationship between depression and lateralized basal ganglia dysfunction is inconclusive. Where differences have been shown, they usually suggest greater depression in patients with right hemiparkinsonism and more marked left-brain disease.

### *Depression and Intellectual Impairment*

Overt dementia with prominent intellectual impairment occurs in approximately 30% of patients with Parkinson's disease. Depression is equally frequent in Parkinson's disease with and without overt dementia (12, 24, 31, 63).

Subtle neuropsychological deficits are common in Parkinson's disease, affecting up to 40% of patients without overt dementia (64). Several investigators have found that patients with Parkinson's disease and depression exhibit more neuropsychological impairment than nondepressed patients with Parkinson's disease. Mayeux et al. (14) and Starkstein et al. (26) found a significant association between depression and deficits on screening mental status examinations. Taylor et al. (19) and Starkstein et al. (65) found that depressed patients with Parkinson's disease performed significantly worse on a number of tasks mediated by frontal lobes or frontal-subcortical systems, and Rogers et al. (66), using reaction time experiments, demonstrated excessive slowing of central processing in patients with Parkinson's disease and depression compared with those without mood changes.

Complete agreement has not been achieved in this area of investigation, but the available studies indicate that patients with Parkinson's disease and depression have more marked frontal lobe dysfunction than those without mood alterations. There may be a common underlying disturbance in frontal-subcortical systems responsible for the depression and the characteristic neuropsychological deficits. Although depression per se could be hypothesized to account for the neuropsychological disturbances observed in depressed patients with Parkinson's disease, comparative studies demonstrate that depression contributes to the memory impairment but not the frontal system abnormalities (65).

### *Depression and the "On-Off" Phenomenon*

The "on-off" phenomenon refers to marked motor fluctuations that occur after chronic L-dopa therapy and includes end-of-dose deterioration occurring as the effect of each administered dose declines as well as unpredictable shifts between mobile or dyskinetic "on" states and akinetic "off" states unrelated to medication

**TABLE 5. Findings of Double-Blind Studies of Antidepressant Treatment for Patients With Parkinson's Disease and Depression**

| Study | Year | Agent | Dose (mg/day) | Number of Subjects | Patients Whose Depression Responded (%) | Effect on Parkinson's Disease | Study Design |
|---|---|---|---|---|---|---|---|
| Strang (5) | 1965 | Imipramine | 150–200 | 20 | 60 | Rigidity improved in 42%, tremor improved in 28%, akinesia improved in 54% | Double-blind |
| Andersen et al. (78) | 1980 | Nortriptyline | 150 | 22 | —[a] | No effect | Double-blind crossover |
| Laitinen (79) | 1969 | Desipramine | 100 | 39 | 50 | Rigidity improved in 25%, tremor improved in 15% | Double-blind |
| Goetz et al. (80) | 1984 | Bupropion | 450 | 20 | 42 | 30% of patients improved | Double-blind followed by open-label phase |

[a] Depression rating scale scores were significantly improved in the active treatment group.

schedules. Numerous investigators (67–73) have documented mood changes—greater depression during akinetic periods—in "on-off" patients. Nissenbaum et al. (72) assessed the frequency and type of mood changes occurring in "on-off" periods. They found that 23% of 136 patients reported having "on-off episodes" and that 68.7% of these described greater depression when "off."

These investigations demonstrate that mood changes are common in patients who experience the "on-off" phenomenon and that depression is commonly exaggerated while patients are in the "off" state. The occurrence of abrupt mood changes in concert with dopamine-mediated motor fluctuations in the "on-off" phenomenon suggests a role for dopamine in mood regulation.

## MOOD EFFECTS OF ANTIPARKINSONIAN TREATMENT

### *Pharmacological Agents*

Pharmacotherapy of the motor deficits of Parkinson's disease exerts little effect on mood. Anticholinergic agents, particularly trihexyphenidyl, have mild euphorigenic effects but are relatively ineffective as antidepressants. Similarly, amantadine has little antidepressant activity.

L-Dopa has limited or no antidepressant efficacy and has occasionally been suspected of producing depression. The frequency of depression reported among patients treated with L-dopa, however, is within the range of that observed in Parkinson's disease before the introduction of L-dopa therapy (8). These observations do not support a marked tendency for L-dopa to increase the frequency of depression, although a role for L-dopa in precipitating or exacerbating mood changes has not been excluded.

Dopamine receptor agonists may have mood-altering effects. Jouvent et al. (74) reported that after 8 days of therapy with bromocriptine, depression ratings of 10 depressed patients with Parkinson's disease had improved 65%. The mood response was more variable than the motor response, and the two did not correlate.

Selegiline, an MAO-B inhibitor thought to slow progression of Parkinson's disease by limiting generation of hydroxyl radicals destructive to neuronal membranes, may have mild antidepressant properties. Ruggieri et al. (75) reported the prevalence of depression in a group of patients to be 35% before the addition of selegiline to their therapeutic regimen and 21% after treatment with the agent. Birkmayer (76) reported that 15% of 1,414 patients with Parkinson's disease treated with L-dopa were depressed; none of 381 patients treated with L-dopa plus selegiline, however, exhibited depressive disorders.

### *Surgical Therapies*

Thalamotomy and pallidectomy are now rarely performed for relief of parkinsonism, but transplantation of adrenal medullary tissue or fetal substantia nigra tissue to the head of the caudate nucleus recently has been introduced as an experimental therapy for Parkinson's disease. The effect of this surgical approach on mood has not been extensively studied. One study (77) found no change from baseline in Beck Depression Inventory scores 6 and 12 months after transplantation in seven patients.

## TREATMENT OF DEPRESSION IN PARKINSON'S DISEASE

### *Pharmacotherapy*

Imipramine, nortriptyline, desipramine, and bupropion have all been shown to be efficacious in the treatment of depression in Parkinson's disease. Table 5 summarizes the doses, treatment responses, effects on Parkinson's disease, and study design of the four available double-blind studies of antidepressants in patients with Parkinson's disease and depression (5, 78–80). Only the study by Andersen et al. (78) used standardized assessments of both depression and Parkinson's disease. These authors observed an effect of nortriptyline on the mood disorder, including improvement in depressed mood, hopelessness, helplessness, and anxiety, but no change in the Parkinson's disease. Imipramine and desipramine were reported to have beneficial effects on both mood and motor abnormalities, and these agents may be more efficacious in relieving Parkinsonian symptoms, but the assessment methodology was less rigorous in these studies. Bupropion, an antidepressant with indirect dopaminergic properties, improved depression in less than half and symptoms of Parkinson's disease in about a third of the depressed patients with Parkinson's disease (80). Mayeux et al. (49) treated seven depressed patients with Parkinson's disease with 5-hydroxytryptophan in an open-label study and observed clinically significant improvement in six. No well-controlled studies using contemporary design technologies have expanded on the earlier studies or addressed the efficacy of other new antidepressants in the treatment of depression in Parkinson's disease.

One study explored the usefulness of psychostimulants in mood changes associated with Parkinson's disease. Cantello et al. (81) found that depressed patients with Parkinson's disease had no euphoric response to intravenous methylphenidate, whereas nondepressed patients with Parkinson's disease, depressed patients without Parkinson's disease, and normal comparison subjects all experienced feelings of euphoria and well-being, talkativeness, psychic activation, and greater locomotor activity. The authors posited the existence of changes in dopaminergic synapses of the limbic system of depressed patients with Parkinson's disease, rendering them incapable of responding to the agent.

Although depression is common in Parkinson's disease and antidepressant agents have demonstrated efficacy in relieving mood disturbances, most studies indicate that depression in Parkinson's disease is undertreated. When reported, the number of patients receiving antidepressant therapy is usually considerably smaller than the number with substantial mood changes (17, 19, 21, 26, 32, 45, 81).

### *ECT*

ECT has also proven to be effective in the amelioration of depression in Parkinson's disease. In most cases, both the mood and the motor syndrome improve, although patients exhibiting ECT-related relief of Parkinson's disease without concomitant mood changes (82) and patients with mood improvement in the absence of a motor response (83) have been reported. All aspects of Parkinson's disease—tremor, rigidity, bradykinesia—improve with ECT, and the motor response usually antedates the mood response in the course of ECT treatments (83–88). The improvement in the motor manifestations of Parkinson's disease is usually short-lived, lasting only a few days or weeks, but is occasionally more sustained (85).

## MECHANISMS OF DEPRESSION IN PARKINSON'S DISEASE

The most daunting challenge in contemporary neuropsychiatry is the translation of neurobiological alterations into models that convincingly relate chemical and structural changes to subjective personal experience. In the case of depression in Parkinson's disease, how do observations regarding pathological and biochemical changes in brainstem nuclei provide insight into the intensely personal experience of sadness, hopelessness, and helplessness? Development of a comprehensive psychiatry embracing both biological and psychosocial domains depends on the ability to construct answers to such questions. Although far from sufficiently comprehensive to define such relationships conclusively, information regarding depression in Parkinson's disease allows construction of a tentative psychobiological model relating neurobiology and behavior.

The morphological changes of Parkinson's disease involve a variety of subcortical nuclei, including the substantia nigra, ventral tegmental area, nucleus basalis, hypothalamus (particularly the lateral and posterior nuclei), pedunculopontine nucleus, dorsal raphe nucleus, locus ceruleus, central pontine nucleus, dorsal motor nucleus of the vagus, and autonomic ganglia (89, 90). There is considerable variability in the severity of involvement of these structures at autopsy: cell loss in the substantia nigra and the locus ceruleus varies from 50% to 85%, in the dorsal raphe nucleus from 0% to 43%, and in the nucleus basalis from 32% to 87% (89). On this basis, substantial heterogeneity in the motor and behavioral manifestations of Parkinson's disease would be predicted.

Subcortical nuclei are major sources of neurotransmitters, and pathological involvement leads to neurochemical depletion remote from the nuclei. The substantia nigra and ventral tegmental area project to the striatum and mesocortical/mesolimbic regions; involvement of these structures in Parkinson's disease results in dopamine depletion in the caudate (75% reduction), putamen (90% reduction), lateral hypothalamus (90% reduction), medial temporal structures (45%–68% reduction), nucleus accumbens (58% reduction), and cingulate cortex (52% reduction) (91). Norepinephrine is reduced 43% in the locus ceruleus, 52% in the substantia nigra, 60% in the nucleus accumbens, and 68% in the posterior hypothalamus (92). Serotonin concentrations are reduced approximately 40% in the caudate nucleus and hippocampus (93) and 40% and 50% in the frontal and temporal poles, respectively (60). High-affinity serotonin binding sites are reduced in the basal ganglia (94). Moderate to marked reductions (up to 70% in some brain regions) in specific neuropeptides also occur in Parkinson's disease, including met-enkephalin, leu-enkephalin, substance P, and bombesin (95). Of these chemical constituents, dopamine, norepinephrine, and serotonin have all been implicated in the pathogenesis of depression in Parkinson's disease. Again, regional variations of involvement, differences in the severity of transmitter depletion, and variable combinations of transmitter loss may contribute to individual differences in the occurrence and severity of mood changes observed in Parkinson's disease.

Transmitter and peptide alterations produce neurophysiological changes relevant to the mediation of mood. The transmitter systems involved in Parkinson's disease mediate reward processes, motivational mechanisms, and stress responses. Dopaminergic neurons of the ventral tegmental area/mesocortical system are a preferred site for self-stimulation in animal experiments, suggesting that the dopamine system plays an important role in reward and reinforcement (96). Febiger (97) hypothesized that the abnormalities in these systems in Parkinson's disease would diminish the effectiveness of reward mechanisms and contribute to anhedonia, loss of motivation, and apathy. Taylor and Saint-Cyr (98) emphasized the important role of forebrain dopaminergic systems in the behavioral functions of expectancy and anticipation. These systems play key roles in motivation and the incentive to act; dysfunction would result in exaggerated environmental dependency with diminished desire to perform activities, decreased sense of personal control, and lessened expectations from one's activities. Clinically, a reduced sense of personal control could manifest as a sense of worthlessness and loss of self-esteem. Environmental dependency and inability to generate activities internally could also spawn feelings of helplessness and hopelessness. Diminished self-efficacy would limit the generation of effective coping strategies, adding to the depression, and patients with Parkinson's disease have been observed to use fewer and less effective coping methods than comparably disabled comparison subjects (99). Experimentally induced stress markedly increases dopamine utilization (96), and dopamine deficiencies in Parkinson's disease might be expected to impair adaptive adjustments to stress and contribute to the dysphoria of depression. Thus, dysfunction of reward-oriented systems could account for anhedonia; prefrontal impairment could explain many of the cognitive elements of the depression syndrome (hopelessness, helplessness, worthlessness, loss of self-esteem); and impairment of the stress response may contribute to the dysphoric experience. Together, these elements constitute the clinical syndrome of depression.

Most of the dysfunctional events described here are mediated by prefrontal dopamine systems, and a series of observations support the hypothesis of greater involvement of these systems in depressed than nondepressed patients with Parkinson's disease. Depressed patients with Parkinson's disease exhibit more frontal-lobe-type neuropsychological deficits, more severe hypometabolism in the frontal lobes when studied with PET, more marked dopamine-based gait and posture abnormalities, an impaired response to a dopamine-receptor-mediated methylphenidate challenge, and more marked involvement of the ventral tegmental area/prefrontal dopaminergic projections at autopsy. The dopamine deficiency would be exaggerated during the "off" state, coinciding with the observed increase in depression during this period. The occurrence and content of depression could be further modified by alterations of noradrenergic and serotonergic systems, opiates, and peptides.

**FIGURE 1. Model of Pathogenesis of Depression in Parkinson's Disease**

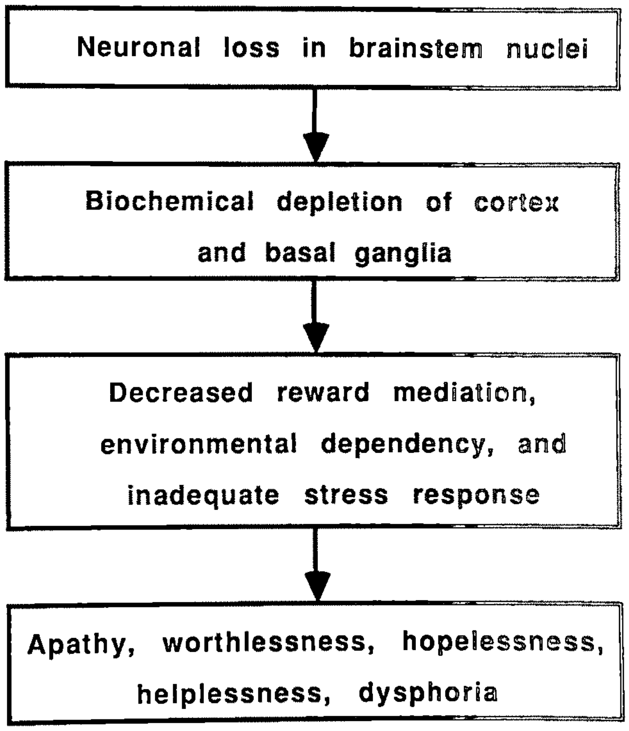
Neuronal loss in brainstem nuclei
Biochemical depletion of cortex and basal ganglia
Decreased reward mediation, environmental dependency, and inadequate stress response
Apathy, worthlessness, hopelessness, helplessness, dysphoria

Figure 1 summarizes the processes potentially contributing to depression in Parkinson's disease. In this tentative model, neuropathological changes leading to transmitter depletion are hypothesized to produce mesocortical and prefrontal dysfunction, with ensuing disruption of "hedonic," motivational, incentive, and stress-alleviating mechanisms and consequent symptoms of worthlessness, helplessness, hopelessness, and dysphoria, recognized as the syndrome of depression. Heterogeneity of the severity of structural involvement, degree of transmitter loss, functional reserve and plasticity of the nervous system, ability to develop effective coping strategies, availability of social supports, and the patient's premorbid personality may all influence the occurrence of the mood changes.

## RESEARCH AGENDA

Several critical areas for research can be identified on the basis of this review. Large-scale demographic studies are needed to establish the prevalence of mood changes in unselected populations of patients with Parkinson's disease. Such studies would also help settle unresolved issues concerning the relationship of depression to age at onset, laterality of Parkinson's disease, and gender. Longitudinal follow-up studies will be required to establish the course of mood changes in Parkinson's disease and to determine if they are characteristic of a limited subgroup of patients with the disease. Combined PET and neuropsychological studies are needed to confirm the association of lower frontal lobe metabolism, cognitive deficits, and mood changes. Well-designed studies of traditional and emerging antidepressants are needed to further define the treatment-response characteristics of depression in Parkinson's disease. Comparative studies of depression in Parkinson's disease with depression in other disorders (e.g., stroke, multiple sclerosis, Huntington's disease) will address the potential existence of disease-specific depression profiles. Autopsy investigations of patients who have been well-characterized clinically are required to illuminate the relationship of mood changes to cellular, transmitter, modulator, and receptor alterations. Synthesis of these data into a comprehensive model will provide insight into the relationship of neurobiological changes to psychiatric syndromes.

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# Is Childhood Sexual Abuse a Risk Factor for Bulimia Nervosa?

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*Objective: It is of considerable theoretical and clinical importance to assess whether childhood sexual abuse is a risk factor for the development of bulimia nervosa. The authors reviewed the scientific literature bearing on this issue. Method: Since prospective studies on this question have not been done, they assessed 1) controlled retrospective studies comparing the prevalence of childhood sexual abuse among bulimic and control groups, 2) uncontrolled retrospective studies of the prevalence of childhood sexual abuse in samples of 10 or more bulimic subjects, and 3) studies of the prevalence of childhood sexual abuse in the general population, which were chosen to match as closely as possible in methodology the available studies of bulimia nervosa (i.e., in geographic location, age and ethnicity of subjects, interview method, and criteria for defining childhood sexual abuse). Results: Controlled studies generally did not find that bulimic patients show a significantly higher prevalence of childhood sexual abuse than control groups, especially when allowance is made for possible methodologic effects. Furthermore, neither controlled nor uncontrolled studies of bulimia nervosa found higher rates of childhood sexual abuse than were found in studies of the general population that used comparable methods. When it is taken into consideration that several methodologic factors might have exaggerated the rates of childhood sexual abuse among subjects with bulimia nervosa relative to rates in the general population, the absence of actual observed differences becomes particularly striking. Conclusions: Current evidence does not support the hypothesis that childhood sexual abuse is a risk factor for bulimia nervosa.*

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Over the last several years, a growing literature has suggested that experiences of childhood sexual abuse may contribute to the development of bulimia nervosa in adolescence or young adulthood. This hypothesis, if confirmed, would have great clinical and theoretical significance, both for our understanding of the etiology of bulimia nervosa and for the development of appropriate treatment strategies for individuals suffering from bulimic symptoms. Thus, the role of childhood sexual abuse in bulimia nervosa deserves careful assessment. This review evaluates the accumulated studies on this subject and suggests avenues for future research.

## STUDIES OF SEXUAL ABUSE AMONG PATIENTS WITH BULIMIA NERVOSA

### *Prospective Studies*

The most satisfactory test for a postulated risk factor in a given disease is the prospective study. Most readers are undoubtedly familiar with classic studies of this design, such as the Framingham Heart Study (1), in which individuals with potential risk factors (elevated serum cholesterol levels, smoking, or obesity) were followed for many years to assess for heart disease. By analogy, a prospective investigation of bulimia nervosa would recruit a large sample of children, document those who experienced instances of childhood sexual abuse, and follow the entire group into adulthood to determine, after controlling for potential confounding variables, whether the abused children ultimately displayed a higher prevalence of bulimia nervosa than matched nonabused children.

To our knowledge, no such study has been conducted, but it is not unreasonable to expect such an investigation in the future. Although difficult and expensive, a prospective study could test the role of childhood

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**TABLE 1. Criteria for Assessing Childhood Sexual Abuse in 14 Studies of Subjects With Eating Disorders and Subjects in the General Population**

| Study | Rating of Study Criteria for Assessing Sexual Abuse[a] | Study Criteria | | |
|---|---|---|---|---|
| | | Childhood Abuse Only | Physical Contact | Older Perpetrator or Clear Coercion |
| Subjects with eating disorders | | | | |
| Hall et al. (2, 3) | Intermediate | Most cases[b] | Yes | No |
| Ross et al. (6) | Intermediate | Yes (<18 years)[c] | Yes[c] | No[c] |
| Stuart et al. (7) | Intermediate | Yes (<18 years) | No[d] | Yes[d] |
| Folsom et al. (9) | Intermediate | Yes (<18 years) | No | Yes |
| | Broad | No | No | No |
| Steiger & Zanko (13) | Intermediate | Most cases[e] | Yes | No |
| Oppenheimer et al. (17) | Intermediate | Yes (<17 years) | No | Yes |
| | Broad | Yes (<17 years) | No | No |
| Sloan & Leichner (18) | Intermediate | No | — | — |
| Bulik et al. (19) | Narrow | Yes (<17 years) | Yes | Yes |
| Root & Fallon (20) | Narrow | Most cases[f] | Yes | Yes |
| Lacey (21) | Narrow | Yes (<18 years) | Yes | Yes |
| Subjects in the general population | | | | |
| Russell (24, 32) | Narrow | Yes (<18 years) | Yes | Yes |
| | Intermediate | Yes (<18 years) | No | Yes |
| Wyatt (33) | Narrow | Yes (<18 years) | Yes | Yes[g] |
| | Intermediate | Yes (<18 years) | No | Yes[g] |
| Bagley & Ramsay (34) | Narrow | Yes (<17 years) | Yes | Yes |
| Finkelhor et al. (35) | Narrow | Yes (<19 years) | Yes | Yes[h] |
| | Intermediate | Yes (<19 years) | No | Yes[h] |

[a] Criteria were rated as narrow if the study required that abuse 1) occur at age 18 or under, 2) involve physical contact, and 3) involve a perpetrator at least 3 years older than the victim and/or clear evidence of coercion. Criteria lacking one of these requirements were rated as intermediate; criteria lacking two or more requirements were rated as broad. If some requirements were unclear, an intermediate rating was assigned.

[b] In 85% of the cases, abuse occurred before age 17 years, but subjects in 15% of the cases were aged 17 years or older.

[c] Personal communication from C. Ross, February 1991.

[d] Personal communication from G. Stuart, March 1991.

[e] Ten percent of the subjects were between the ages of 15 and 20 at the time of the abuse.

[f] No specific age criterion was used, but most cases of abuse occurred before age 14 (personal communication from P. Fallon, March 1991).

[g] Coercion was required if the perpetrator was less than 5 years older than the victim.

[h] Although a formal requirement of age difference was not included, only 4% of victims reported perpetrators less than 4 years older than themselves.

sexual abuse not only as a risk factor for bulimia nervosa but also for the entire spectrum of other psychiatric disorders, thus yielding a great deal of information in return for the investment.

### *Controlled Retrospective Studies*

Given the obvious difficulty of performing a prospective study of sexual abuse, it seems only reasonable to admit the evidence of other less methodologically sophisticated study designs. Of these, the best are controlled retrospective studies, in which a group of bulimic patients (or, more often in practice, patients with anorexia and/or bulimia nervosa) is compared with a group of control individuals. The latter must, of course, be matched as closely as possible in age, sex, and other demographic attributes that may be correlated with the prevalence of childhood sexual abuse.

Six such studies are known to us. In the first, Hall et al. (2, 3) compared 56 bulimic and 16 anorexic patients with a control group of 86 other patients admitted to the same unit but apparently assessed by "colleagues treating adolescents for other reasons on an adolescent treatment unit" (3). Sexual abuse was assessed by "clinical interview and subsequent therapeutic interventions" (2); it was apparently defined to include only events involving physical contact between perpetrator and victim (table 1). Twenty-eight (50%) of the 56 bulimic patients (table 2) and eight (50%) of the 16 anorexic patients were rated as having experienced sexual abuse, compared with 24 (28%) of the control subjects. The rate of sexual abuse in the bulimic and anorexic groups combined was reported to be significantly higher than in the control group ($p<0.01$).

However, the authors apparently failed to match their control group for sex. They stated that 98% of the anorexic and bulimic patients were female (3) and also that 98% of all of the abused patients were female (2); but only 85% of the nonabused patients were female (2). Therefore, at least 14 of the control patients were male, in comparison with only one of the patients with eating disorders. When the control group is corrected to be sex-matched with the eating disorder group, the difference between groups in the prevalence of sexual abuse is no longer significant.

Second, the authors noted that in 15% of the cases, sexual abuse occurred at age 17 or above. Since bulimia and anorexia nervosa commonly begin in adolescence (4), it seems likely that in at least some cases, sexual abuse began after the onset of the eating disorder. While their importance should not be denied, these particular instances of abuse cannot be credited toward the

**TABLE 2. Prevalence of Childhood Sexual Abuse Among Subjects With Eating Disorders and Subjects in the General Population in 14 Studies**

| | | | Subjects With Sexual Abuse[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | According to Narrow Criteria | | According to Intermediate Criteria | | According to Broad Criteria | |
| Study | N | Diagnosis | N | % | N | % | N | % |
| Subjects with eating disorders | | | | | | | | |
| Hall et al. (2, 3) | 56 | Bulimia | | | 28 | 50 | | |
| Ross et al. (6) | 20 | Anorexia or bulimia | | | 4 | 20 | | |
| Stuart et al. (7) | 30 | Bulimia | | | 15 | 50 | | |
| Folsom et al. (9) | 102 | *DSM-III* eating disorders | | | 47 | 46 | 70 | 69 |
| Steiger & Zanko (13) | 45 | Bulimia | | | 16 | 36 | | |
| Oppenheimer et al. (17) | 33 | Bulimia | | | 8 | 24 | 22 | 67 |
| Sloan & Leichner (18) | 23 | *DSM-III* eating disorders | | | 9 | 39 | | |
| Bulik et al. (19) | 35 | Bulimia | 10 | 29 | | | | |
| Root & Fallon (20) | 172 | Bulimia | 49 | 28 | | | | |
| Lacey (21) | 112 | Bulimia | 8 | 7 | | | | |
| Subjects in the general population | | | | | | | | |
| Russell (32) (ages 18–36 only) | 470 | | 200 | 43 | 276 | 59 | | |
| Wyatt (33) | | | | | | | | |
| Entire sample | 248 | | —[b] | 45 | 154 | 62[c] | | |
| White women only | 122 | | —[b] | 51 | 82 | 67[c] | | |
| Bagley & Ramsay (34) (under age 40 only) | 134[d] | | —[b] | 28 | | | | |
| Finkelhor et al. (35) (ages 18–39 only) | 670 | | —[b] | 27 | —[b] | 31 | | |

[a] Criteria were rated as narrow if the study required that abuse 1) occur at age 18 or under, 2) involve physical contact, and 3) involve a perpetrator at least 3 years older than the victim and/or clear evidence of coercion. Criteria lacking one of these requirements were rated as intermediate; criteria lacking two or more requirements were rated as broad. If some requirements were unclear, an intermediate rating was assigned.

[b] N not provided by authors.

[c] If peer abuse cases are deleted entirely, the rates according to intermediate criteria decline only slightly, to 59% for the entire sample and 65% for the white women only.

[d] This figure is an approximation calculated from the authors' table 1.

hypothesis that sexual abuse is a risk factor for eating disorders.

A third possible methodologic limitation of this study is in its methods of assessing sexual abuse. It is not clear whether control patients were evaluated as extensively for sexual abuse as were the anorexic and bulimic patients and whether the two groups were evaluated by the same person or persons. Although a "structured questionnaire" was mentioned in one of the two reports of the study (3), it was not described.

By contrast, a structured diagnostic interview of established reliability, the Dissociative Disorders Interview Schedule (5) was used by Ross et al. (6) in the second controlled retrospective study that we reviewed. These authors assessed sexual abuse, among many other variables, in 20 patients with anorexia or bulimia nervosa, 20 with panic disorder or agoraphobia, 20 with schizophrenia, and 20 with multiple personality disorder. All groups were recruited from specialized clinics at the same center, and more than 85% of the consecutive subjects in each group agreed to participate in the study. By the criteria of the Dissociative Disorders Interview Schedule, four (20%) of the anorexic and bulimic patients were rated as having experienced childhood sexual abuse (table 2)—a rate not significantly different from the rate of 10% in the groups with anxiety disorders and schizophrenia. Further, since all of the patients with eating disorders were female, whereas 15% of the patients with anxiety disorders and 70% of the schizophrenic patients were male, these small differences may be partially due to sex distribution. By contrast, 16 (80%) of the patients with multiple personality disorder reported sexual abuse, a significantly higher rate than that of the patients with eating disorders ($p<0.0005$).

The two studies we have mentioned so far, it might be argued, may have failed to reveal an association between sexual abuse and bulimia nervosa because the control groups were also composed of psychiatric patients. Of course, to make this argument, one would have to posit that most or all of the various psychiatric disorders of subjects in the control groups were themselves associated with sexual abuse—a broader assumption. In this context, the next two studies are of interest, since they used nonpsychiatric populations.

In the first of these, Stuart et al. (7) compared 30 bulimic women and 15 depressed women, recruited from the clinical research section at their center, with 100 sociodemographically matched control women. The control women were not a random population but "supernormal": they were required to have no psychiatric diagnosis, to have never sought psychiatric treatment, and even to have no first-degree relatives with psychiatric diagnoses. Sexual abuse was assessed by a written victimization inventory modified from the original Crime Victimization Inventory (8). On this scale, no significant difference was found between the bulimic subjects and either of the other two groups on any of the measures of sexual mistreatment, although there was a trend on the item of sexual molestation, reported by 50% of the bulimic subjects (table 2) and 40% of the depressed subjects, compared with 28% of the normal control subjects.

This trend, however, may be an artifact of the use of supernormal control subjects in the study design, as can be illustrated by a medical analogy. Consider a comparison of the prevalence of smoking by patients with rheumatoid arthritis and a control group of age-matched patients screened to show no medical illness of any type. The prevalence of smoking would almost certainly be lower in the supernormal control subjects in such a comparison, leading to the erroneous conclusion that smoking is associated with rheumatoid arthritis. When it is considered that the control subjects in the Stuart et al. study were screened to exclude not only personal psychiatric disorder but even familial psychiatric disorder, a similar effect seems possible.

In the fourth and largest controlled retrospective study, Folsom et al. (9, and personal communication from V. Folsom, February 1991) compared 102 female inpatients with eating disorders (57 with bulimia nervosa, 17 with anorexia nervosa, 19 with both disorders, and nine with eating disorders not otherwise specified, according to *DSM-III-R*), 49 general psychiatric inpatients with a wide range of other *DSM-III-R* axis I diagnoses, and 44 college and graduate student control subjects. The instruments they used were the Finkelhor Sexual Life Events Questionnaire (10), the Eating Disorders Inventory (11), and the SCL-90 (12). Personal interviews were not administered. When the results were analyzed, only the broadest definition of sexual abuse revealed a significant difference between groups (general psychiatric patients, 81%; patients with eating disorders, 69% [table 2]; college and graduate students, 48%). Looking only at sexual abuse that occurred before the age of 18, the authors found no significant differences between the patients with eating disorders and the other two groups on any of the various comparisons they performed. In addition, among the patients with eating disorders, a history of sexual abuse was not significantly associated with higher scores on any of the eight subscales of the Eating Disorders Inventory.

In this study, as in the preceding one, it must also be recognized that the control group represented to some extent supernormal individuals; women admitted to college and graduate school are a selected and successful group who might well have a lower prevalence of sexual abuse than an entirely random population. Therefore, the already nonsignificant differences between the patients and the control subjects might be further reduced if allowance were made for the possibility that data from college and graduate students underestimate the prevalence of childhood sexual abuse in the population at large.

Steiger and Zanko (13) examined populations similar to those of the previous study: 73 women with eating disorders (28 with anorexia nervosa and 45 with bulimia nervosa according to *DSM-III-R* criteria); 21 psychiatric comparison subjects with affective (N=8), anxiety (N=7), adjustment (N=2), personality (N=3), and schizophrenic (N=1) disorders; and 24 normal control subjects obtained from among the hospital staff, patients' friends, and students. Data on sexual abuse was elicited by a brief self-report questionnaire, without personal interview. The criteria for sexual abuse were thus somewhat vague, since subjects were free to use their own interpretation of various terms on the questionnaire, such as "inappropriate touching." Sexual abuse was reported by six (21%) of the anorexic patients, 16 (36%) of the bulimic patients (table 2), and seven (33%) of the psychiatric comparison subjects, but by only two (9%) of the 23 normal control subjects assessed.

Although no difference in the rate of sexual abuse was found in this study between the bulimic patients and the psychiatric patients without eating disorders, the difference between the bulimic patients and the normal control subjects was significant ($p=0.03$ by Fisher's exact test, two-tailed). However, the 9% rate of sexual abuse reported by the normal control subjects in this study seems peculiarly low: in the previous two studies reviewed, normal control subjects displayed rates of 28% and 48%. One possible explanation for this discrepancy may be that normal control subjects in the Steiger and Zanko study included hospital staff and possibly other individuals known socially or occupationally to the authors. Since the questionnaire was apparently not anonymous, these individuals may have been reluctant to reveal instances of sexual abuse in their personal lives.

A sixth controlled study used a "reverse" design: it compared sexually abused and nonabused women for their current and lifetime prevalences of eating disorders. In this study, Finn et al. (14) administered a sexual abuse screening checklist to 87 women recruited from a variety of psychotherapy groups. Patients checking "yes" or "unsure" on any item on this checklist (N=71, or 82%) were subsequently administered a structured interview about sexual abuse by interviewers who had established good interrater reliability with this instrument. Sixty-one women were rated as abused. "Abuse" was defined to require actual sexual contact but included instances of contact with a physician or therapist as well as the more usual categories of abusers. Eating disorders were assessed by an Eating Patterns Questionnaire previously developed and published by the same group (15). Although subjects were not reassessed for eating disorders by personal interview, the questionnaire appeared reliable: two raters independently rated 10 Eating Patterns Questionnaires and generated 100% agreement on all diagnostic ratings.

No significant difference or, apparently, even trend toward a significant difference, was found between the 61 abused and 26 nonabused women in the prevalence of current bulimia nervosa, of lifetime bulimia nervosa, or of current or lifetime episodes of more broadly defined bulimic behaviors (including binge eating, vomiting, and severely restrictive dieting). Two further analyses—the first redefining abuse to include only instances of direct genital contact and the second comparing subjects with incestuous abuse, subjects with nonincestuous abuse, and nonabused control subjects—also failed to show significant differences between any of the groups on any of the diagnostic categories of eating disorder examined. The authors speculated that clinicians might perceive an "illusory correlation" between sexual abuse and eating disorders because each of these phenomena is so common that frequent co-occurrence would be expected by chance alone. They cited a study of bias in clinical judgment (16) which notes that people tend to base their estimate of covariation on observed instances of co-occurrence of the variables in question, while tending to ignore instances in which one variable occurs in the absence of the other.

Thus, of the six controlled retrospective studies that we reviewed, four found no significantly greater prevalence of childhood sexual abuse among bulimic patients (or, in one case, prevalence of bulimic behaviors among sexually abused patients) in any of their comparisons with control subjects. The fifth study found a significantly higher prevalence of sexual abuse in anorexic and/or bulimic patients than in control subjects, but after sex matching, this difference also fails to reach significance. The sixth study found a significant difference between bulimic patients and normal control subjects, but this difference may reflect the atypically low rate of sexual abuse found in the control group.

### *Uncontrolled or Anecdotal Studies*

Several uncontrolled studies of sexual abuse among bulimic patients have also appeared. Those with samples of 10 or more bulimic patients are reviewed here.

Oppenheimer et al. (17) administered a written questionnaire, followed by a verbal interview, to 78 consecutive women with eating disorders presenting at a clinic. Of these women, 33 met the *DSM-III* criteria for bulimia, 36 met the criteria for anorexia nervosa, and nine were "mixed." Adverse sexual events were defined in the manner of the 1979 study of Finkelhor (10), a relatively broad definition that included noncontact experiences such as "an invitation or request to do something sexual." By these criteria, eight (24%) of the bulimic women and 23 (29%) of the entire sample reported sexual abuse. Eleven of the 78 subjects failed to complete the questionnaire; since it is likely that some of these subjects had experienced sexual abuse, the resulting figures may be conservative. When the authors expanded their criteria further to eliminate the age-difference criterion (shown in the second line for the Oppenheimer et al. study in our table 1), the prevalence rose to 22 (67%) of the bulimic patients (table 2) and 50 (64%) of the entire sample.

Sloan and Leichner (18), in a primarily anecdotal report, described five cases of inpatient women with eating disorders who, in the course of treatment, revealed histories of childhood sexual abuse. All of these cases would meet rigorous or narrow criteria for childhood sexual abuse, since they involved contact by a perpetrator older than the subject. At the end of the study, the authors noted that nine (39%) of 23 subsequent new inpatients on the same unit reported past or present sexual abuse or incest (table 2). It is not clear how many of these nine cases met a narrow definition, or how many were past experiences and how many were in the present and thus occurred only after the onset of bulimia nervosa.

Bulik et al. (19) examined 35 women meeting the *DSM-III* criteria for bulimia who were recruited during an investigation of family environment and psychiatric history. On structured interviewing, 10 (29%) reported childhood sexual abuse that met narrow criteria (table 2); two other subjects came from families in which incest had occurred, but they had not been victims themselves. This study is particularly interesting because it provides diagnoses for the perpetrators in most instances; in at least five of the 10 cases, the perpetrator had a diagnosis of alcohol dependence, bipolar disorder, or both.

Root and Fallon (20) interviewed 172 consecutive female applicants to a bulimia treatment program, all of whom met the *DSM-III* criteria for bulimia. Criteria for sexual abuse were narrow (personal communication from P. Fallon, March 1991). Forty-nine (28%) of the patients were found to have been sexually abused (table 2). An additional 23 subjects reported rape, but it appears that many or all of these subjects were raped as adults. Thus, most rapes probably occurred after the onset of bulimia.

Lacey (21) personally interviewed 112 consecutively referred women who met the *DSM-III-R* criteria for bulimia nervosa. Toward the end of the 3-hour interview, he asked a series of questions regarding childhood sexual abuse. Using rigorous, narrow criteria, he found that eight (7%) reported such experiences (table 2). One, however, did not experience sexual abuse until 1 1/2 years after the onset of her binge eating. Although the prevalence rate found in this study is lower than that reported in other studies, the author argued that it is unlikely that actual cases of sexual abuse were missed, since most patients subsequently entered psychotherapy with female therapists, and no further cases came to light.

One relevant study is not easily classified in the categories we have mentioned. Calam and Slade (22) analyzed the responses of 130 undergraduate college women on the Eating Attitudes Test (23) and a Sexual Events Questionnaire derived from that of Russell (24). It is important to note that the latter instrument contained questions about both childhood and adult sexual events. No significant correlation was found between the number of childhood sexual events (defined as occurring before age 14) and total score on the Eating Attitudes Test or scores on the dieting and bulimia subscales of that test. Answers to five of the six questions about childhood events on the Sexual Events Questionnaire also showed no correlations with total or subscale scores on the Eating Attitudes Test. Only one item, early sexual intercourse against the participant's wishes, showed significant though modest correlations (i.e., with the bulimia subscale scores, r=0.18, which would explain 3% of the variance).

When adult events were added in, several significant correlations did appear, but these are less relevant to the purposes of our review because of the possibility, discussed earlier, that many such events may have occurred after the onset of bulimia nervosa. It should be noted, however, that even with the addition of adult events, there was still no significant association between either total sexual events or intrafamilial sexual events and scores on the bulimia subscale of the Eating Attitudes Test.

Finally, it should be noted that several other studies have assessed sexual abuse in various series of bulimic patients (25–30) or patients displaying bulimic behaviors (31). However, these studies cannot be compared directly with the studies we have summarized because they either have not been published in full or provide insufficient data to permit an estimate of the overall prevalence of sexual abuse in the bulimic groups they examined. Thus, they are acknowledged but not summarized in this review.

## STUDIES OF SEXUAL ABUSE IN THE GENERAL POPULATION

Given that few of the studies of bulimic patients had access to a control group of unselected, nonpatient women, it is instructive to examine for comparison some of the large studies of childhood sexual abuse in the general population. To ensure comparable methods across studies, we sought general population studies of sexual abuse that 1) were published, 2) were conducted in the United States, Canada, or the United Kingdom (the three countries where the bulimia studies we have mentioned were conducted), and 3) assessed the history of sexual abuse in all subjects by personal interview (as did all but three [7, 9, 13] of the bulimia studies we have reviewed). We found four large studies meeting these three criteria.

Russell (24, 32) examined a probability sample of 930 San Francisco women, using trained interviewers to administer a detailed questionnaire devoted to adverse sexual experiences. Remarkably, 357 (38%) of these women reported incestuous and/or extrafamilial sexual abuse involving physical contact before age 18; this figure rose to 504 (54%) when noncontact experiences were included. However, when analysis was restricted to women 18–36 years of age (an age range more closely comparable to that of bulimic patients in most studies), the figures were even higher: 43% for contact experiences and 59% for noncontact experiences (32) (table 2). Strikingly similar findings were subsequently reported by Wyatt (33), who conducted lengthy interviews with a probability sample of 248 African-American and white women, aged 18–36 years, in Los Angeles: 45% reported contact experiences and 62% noncontact experiences (table 2). If one looks exclusively at the data for the 122 white women in this study (a subsample more closely matched to the predominantly white composition of most bulimia groups), the figures are even higher: 51% and 67%, respectively. Bagley and Ramsay (34) studied 377 women representing a probability sample drawn from Calgary, Alta., Canada, as part of the follow-up of a mental health survey. At the end of an extensive interview regarding many aspects of mental health, the interviewers asked several questions about sexual abuse, which was narrowly defined. Of the women under 40 years of age, 28% reported such abuse (table 2). Ten additional women in the study answered "yes" to the initial question regarding "a serious sexual assault by an older person" but were unwilling to elaborate. These individuals were not included in the 28% figure.

Most recently, Finkelhor et al. (35) reported on a national telephone survey of 1,145 men and 1,481 women in the United States in which subjects were asked four specific questions about sexual abuse; the interviewers apparently had no specific training in this area or in psychiatry as a whole. Thus, the prevalence rates generated in this study might again be expected to be lower than would be elicited in face-to-face interviews by trained interviewers, as in the Russell and Wyatt studies. Nevertheless, the rate of sexual abuse elicited was 31% among women 18–39 years of age and remained at about 27% even when noncontact experiences were excluded (table 2).

In summary, then, among randomly chosen women comparable in age to those in groups of bulimic subjects, these four interview studies produced prevalence rates of 27%–51% for narrowly defined childhood sexual abuse by an older perpetrator and 31%–67% if noncontact experiences are included. The two studies that used detailed, face-to-face interviews by trained interviewers produced the highest figures, suggesting that the true prevalence of childhood sexual abuse in the general population may lie closer to the upper end of these ranges. For bulimic patients, as shown in table 2, reported prevalence rates fall well within the same ranges as those for the general population.

Although table 2 shows no differences in the prevalence of childhood sexual abuse between bulimic patients and the general population, it might still be argued that when abuse did occur, it was more severe, more protracted, or occurred at an earlier age in the former group (31, and personal communication from R. Pyle, March 1991). This possibility can be neither accepted nor rejected on the basis of published studies to date. However, given that bulimic patients apparently do not differ from the general population when intermediate or narrow definitions of sexual abuse are used, the burden of proof rests on those who suggest that a difference would nevertheless emerge with use of a very narrow definition, i.e., unusually severe or repeated abuse.

## METHODOLOGIC CONSIDERATIONS

The lack of differences in the prevalence of childhood sexual abuse between bulimic patients and the general population becomes even more impressive when it is considered that there are at least four potential sources of bias in studies of this nature, all of which might be expected to skew the findings in favor of higher abuse rates for bulimic patients than for control subjects. These factors are the following.

1. Detail of the information. Some of the studies of bulimic patients (2, 3, 18) derived information about sexual abuse from multiple interviews over a period of time during treatment, whereas the general population studies we have cited used never more than a single interview (24, 32, 33), and in two studies (34, 35), only a few questions. Given that a patient may not reveal a history of sexual abuse until she or he has formed a trusting relationship with a therapist—sometimes only after years of treatment (18)—it seems that the single-interview population studies might find lower rates of abuse than studies of bulimic patients in treatment, even if the two rates were actually the same.

A corollary consideration is that some individuals might have amnesia or "screen memories" for traumatic experiences of sexual abuse, causing the investigator to miss true cases. However, this source of error would affect individuals in the general population as well as patients with bulimia nervosa, and the latter, through their experience in therapy, might be more successful in retrieving suppressed memories than would untreated control subjects receiving only a single interview.

2. Lack of blind assessment. In only one study to date (19) were bulimic subjects assessed for sexual abuse by an individual blind to the diagnosis of eating disorder. Since most investigators presumably suspected a link between bulimia nervosa and sexual abuse, nonblind conditions leave open the risk that a rater might have unconsciously elicited or scored more sexual abuse for bulimic subjects than for persons known to be control subjects.

3. Effort after meaning. In a so-called "effort after meaning," patients with psychiatric disorders frequently search their past lives for some explanation of their distress (36). In one study, for example, 50% of depressed patients identified a life event or stressor as a cause of their condition, but after detailed clinical evaluation, this stressor was found to be a plausible cause in only 9% of the cases (37). By analogy, bulimic patients, particularly those who become aware of the sexual abuse hypothesis, may be more likely to remember and/or report childhood sexual abuse than control individuals who have less impetus for effort after meaning.

4. Familial psychiatric disorder. Family studies of bulimia nervosa have generally found substantially elevated rates of alcohol abuse and major mood disorders in the relatives of bulimic probands (38–43). Regardless of whether this phenomenon is genetic or environmental in origin, it seems that relatives with alcoholism or mood disorders would be more likely to abuse a child sexually than would relatives without psychiatric disorder. Indeed, in the study by Bulik et al. (19), as mentioned earlier, at least five of the 10 sexually abused bulimic patients were victimized by a relative with alcohol dependence and/or bipolar disorder. Therefore, even if bulimia nervosa were not *caused* by sexual abuse, one would still expect bulimia nervosa to be more frequently *associated* with sexual abuse because of the known association between bulimia nervosa and these familial psychiatric disorders. To argue that sexual abuse causes bulimia nervosa, one would have to demonstrate an elevated prevalence of sexual abuse among bulimic patients even after matching the control subjects for prevalence of familial alcoholism and mood disorder.

In summary, the four methodologic problems we have listed should be considered in the evaluation of any study of sexual abuse among persons with bulimia nervosa, since each would seem likely to bias the results in favor of a higher prevalence of childhood sexual abuse among these persons than among control subjects. Future studies should be designed to address these problems. A prospective study, for example, would almost automatically resolve problems 1–3 and could be constructed to address problem 4 at least partially. Future studies should also attend to the unresolved question, mentioned earlier, of whether particularly severe forms of sexual abuse, more prolonged abuse, or abuse occurring at a younger age might be more prevalent among those who develop bulimia nervosa than among those who do not.

## CONCLUSIONS

For both clinical and theoretical reasons, it is important to assess whether childhood sexual abuse is a risk factor for bulimia nervosa. To address this question, we attempted to review all quantitative studies of childhood sexual abuse among patients with bulimia nervosa, including both controlled and uncontrolled designs. We also reviewed methodologically comparable studies of childhood sexual abuse in the general population in order to compare these results with those for persons with bulimia nervosa.

Of six controlled studies, four found no significantly higher rating on any measure of childhood sexual abuse among bulimic subjects than among control subjects. The fifth study found a significantly higher prevalence of sexual abuse among bulimic patients than among control subjects, but when corrected for sex distribution, this difference also becomes nonsignificant. A sixth study found a significant difference between bulimic patients and normal control subjects, but the rates in the control group in this study were much lower than those in other studies.

Several uncontrolled studies have also reported high rates of childhood sexual abuse for bulimic patients. However, if one examines general population studies that used comparable methods, taking care to match definitions of sexual abuse as closely as possible, it emerges that rates of sexual abuse reported in the various studies of patients with bulimia nervosa compare closely to the range of rates reported in the population at large.

In addition, one must also take into consideration at least four methodologic factors in the designs of available studies which would be expected, if anything, to inflate the rate of childhood sexual abuse among patients with bulimia nervosa relative to that in the general population. Given these factors, the absence of elevated rates of childhood sexual abuse for patients with bulimia nervosa becomes even more striking. Thus, current evidence does not support the hypothesis that childhood sexual abuse is a risk factor for bulimia nervosa.

These conclusions should not be interpreted to mean that childhood sexual abuse is an unimportant issue in the therapy of bulimic patients. Such issues may be very important, but the therapist should be wary of the assumption that the abuse is the cause of bulimia nervosa or that treatment addressing the abuse will necessarily alleviate bulimic symptoms. It may be more profitable, both in therapy and in research, to direct our search toward other potential causes of bulimia nervosa and, perhaps even more urgently, toward understanding the origins of the high levels of childhood sexual abuse that apparently exist in our society as a whole.

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# Nicotine Withdrawal Symptoms and Psychiatric Disorders: Findings From an Epidemiologic Study of Young Adults

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*Objective: Earlier, the authors reported on the association of nicotine dependence with major depression and anxiety disorders in a group of young adults. This report describes the occurrence of withdrawal symptoms and their sociodemographic and psychiatric correlates in persons in that group who tried unsuccessfully to abstain from smoking. Method: A random sample of 1,007 members of a health maintenance organization, 21–30 years old, were interviewed with a revised version of the NIMH Diagnostic Interview Schedule. Data on nicotine withdrawal came from a subset of 239 smokers who had tried unsuccessfully to quit or cut down on smoking. Results: With two exceptions, each of the DSM-III-R nicotine withdrawal symptoms was reported by more than one-half of these smokers. Withdrawal symptoms were more severe in white than in black smokers but were unrelated to sex, educational level, or marital status. Persons with histories of major depression or any anxiety disorder reported more severe withdrawal symptoms than persons with neither of these disorders. Severity of withdrawal, or any specific symptom, did not account for the association between major depression and continued smoking. Furthermore, severity of withdrawal was unrelated to continued smoking. Conclusions: While the long-term clinical significance of nicotine withdrawal is unclear, the evidence indicates that in the general population, abstinence from smoking is associated with a variety of disturbances, including a craving for cigarettes, dysphoria, and symptoms of irritability or nervousness. In this study disturbances were more severe in persons with histories of major depression or anxiety disorders.*

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Although the discomfort of withdrawal is presumed to play a role in preventing cessation of drug use (1), the empirical support for this relationship among smokers is inconsistent (2–8). Little is known about factors associated with nicotine withdrawal symptoms in the general population. Studies of clinical samples have provided inconsistent findings on gender differences. While some studies have reported that women have more withdrawal symptoms than men, other studies have found no sex differences in severity of withdrawal (3, 4, 8). No associations have been found between withdrawal symptoms and age, marital status, educational level, or other socioeconomic status indicators (4). In contrast, two recent reports have suggested that smokers with histories of major depression experience more of the defining symptoms of nicotine withdrawal or more psychological distress, anger, and other disturbances that characterize withdrawal (7, 9). The greater withdrawal discomfort observed in persons with histories of major depression has been proposed as

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the mechanism that accounts for the higher rates of smoking and lower rates of quitting among persons with depressive symptoms or major depression (7, 10–13).

Recently, we reported on the association of nicotine dependence, as defined in *DSM-III-R,* with major depression and anxiety disorders in an epidemiologic sample of young adults in the Detroit area (13). The study used the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (14), revised according to *DSM-III-R,* to ascertain psychiatric and substance use disorders, smoking histories, and nicotine withdrawal symptoms. Persons with histories of nicotine dependence had higher lifetime rates of major depression and any anxiety disorder than persons who had never been nicotine dependent. Further, a history of major depression increased significantly the likelihood of continued smoking within the year preceding the interview. A history of any anxiety disorder was not associated with the persistence of smoking.

In this report, we examine the association of nicotine withdrawal with major depression and any anxiety disorder in this sample of young adults. The following questions are addressed. 1) What are the rates of individual nicotine withdrawal symptoms in a sample of the general population of young adults? 2) Does severity of withdrawal, defined by number of symptoms, vary by sex, race, educational level, or marital status? 3) Do persons with histories of major depression, an anxiety disorder, or alcohol or illicit drug abuse/dependence report more severe nicotine withdrawal or higher rates of specific withdrawal symptoms? 4) Does severity of withdrawal symptoms account for the association between a history of major depression and continued smoking?

## METHOD

The sample and method of measurement have been described in detail previously (13). Briefly, a random sample of 1,007 members of a large health maintenance organization in the Detroit area, who were 21–30 years old, were interviewed in 1989 with the DIS, revised to cover *DSM-III-R* diagnoses. Of the total sample, 61.7% (N=621) were female, 80.7% (N=813) were white, and 29.3% (N=295) were college graduates. Three hundred ninety-four (39.1%) of the respondents reported that they had smoked daily for a month or more at any time in their lives and were defined as smokers. Smoking daily for a month or more during the year preceding the interview was defined as continued smoking.

Information on withdrawal symptoms was elicited from all smokers who had ever tried unsuccessfully to quit or cut down on smoking. The revised DIS elicits information on the occurrence of 12 symptoms in the first day or so after quitting or cutting down. The list includes the defining symptoms of nicotine (or tobacco) withdrawal in both *DSM-III* and *DSM-III-R*. In addition, two symptoms not included in either *DSM*—tremor and feeling depressed—were included as experimental items.

The associations of a lifetime history of major depression and a lifetime history of any anxiety disorder with severity of withdrawal, measured by total number of withdrawal symptoms, were tested by using multiple regression analyses in which alcohol abuse/dependence and drug abuse/dependence were included as covariates. The unstandardized regression coefficients estimate the increase in withdrawal symptoms associated with each disorder independent of the other disorder and these covariates.

To examine whether nicotine withdrawal symptoms accounted for the association between major depression and continued smoking, a hierarchical multivariable logistic regression analysis was used. Two successive regressions were calculated. The first regression estimates the logistic odds for continued smoking associated with major depression, controlling for any anxiety disorder. The second regression adds the number of withdrawal symptoms to the equation and recalculates the logistic odds for continued smoking associated with major depression. A comparison of the coefficients of major depression in the first and second regressions can show whether withdrawal symptoms act as an intervening mechanism between major depression and continued smoking. Specifically, a marked reduction in the coefficient of major depression from the first to the second regression would support the proposition that withdrawal symptoms explain why those who have histories of major depression are more likely to continue to smoke than those without such histories. The exponential transformation of the logistic odds, calculated in the logistic regression, yields the odds ratio. The odds ratio estimates the multiplicative factor by which the dependent variable (i.e., continued smoking) is increased in persons with the suspected risk factor (i.e., history of major depression). An odds ratio greater than 1 indicates a greater rate of continued smoking among smokers with histories of major depression than among smokers with no prior history of major depression.

## RESULTS

Of the 394 persons who had ever smoked daily for a month or more, 241 (61.2%) reported that they had tried unsuccessfully at least once to quit or cut down on smoking. Information on the occurrence of each of 12 symptoms in the first day after quitting or cutting down on the number of cigarettes appears in table 1. (The analysis is for the 239 respondents for whom there were complete data on the relevant variables.) The rates of symptoms ranged from less than 10% (decreased heart rate, upset stomach) to 82% (craving for cigarettes). Of the seven symptoms that define nicotine withdrawal in *DSM-III-R,* that is, symptoms 1–7 in table 1, five were reported by more than 50% of the smokers who had tried unsuccessfully at least once to quit or cut down. In contrast, trouble concentrating was reported by 27.2%

**TABLE 1. Withdrawal Symptoms in 239 Smokers Who Had Tried Unsuccessfully to Quit or Cut Down**

| Symptom | N | % |
|---|---|---|
| Craving for cigarettes | 196 | 82.0 |
| Irritability | 147 | 61.5 |
| Nervousness | 120 | 50.2 |
| Trouble concentrating | 65 | 27.2 |
| Restlessness | 136 | 56.9 |
| Decreased heart rate | 23 | 9.6 |
| Increased appetite | 143 | 59.8 |
| Headache | 43 | 18.0 |
| Drowsiness | 31 | 13.0 |
| Upset stomach | 21 | 8.8 |
| Tremor | 39 | 16.3 |
| Feeling depressed | 54 | 22.6 |

**TABLE 2. Number of Withdrawal Symptoms in 239 Smokers Who Had Tried Unsuccessfully to Quit or Cut Down**

| | | Number of Symptoms | |
|---|---|---|---|
| Variable | N | Mean | SD |
| Sex | | | |
| Male | 86 | 3.93 | 2.12 |
| Female | 153 | 4.39 | 2.23 |
| Race[a] | | | |
| White | 209 | 4.40 | 2.17 |
| Black | 30 | 3.00 | 2.02 |
| Education | | | |
| College | 31 | 4.53 | 2.37 |
| Less than college | 208 | 4.18 | 2.18 |
| Marital status | | | |
| Married | 114 | 4.50 | 2.15 |
| Never married | 102 | 3.95 | 2.13 |
| Divorced/separated | 23 | 4.04 | 2.62 |

[a] t=3.32, df=237, p=0.001.

**TABLE 3. Relation Between Number of Withdrawal Symptoms and History of Psychiatric Disorders in 239 Smokers Who Had Tried Unsuccessfully to Quit or Cut Down**

| | | Number of Symptoms | |
|---|---|---|---|
| Disorder | N | Mean | SD |
| Major depression | 59 | 5.17 | 2.10 |
| Any anxiety disorder[a] | 110 | 4.84 | 2.11 |
| Alcohol abuse/dependence | 69 | 4.86 | 2.11 |
| Drug abuse/dependence | 58 | 4.47 | 2.48 |
| No disorder[b] | 73 | 3.60 | 2.02 |

[a] Includes panic disorder, phobia, obsessive-compulsive disorder, generalized anxiety disorder, and posttraumatic stress disorder.

[b] Includes persons with no history of affective, anxiety, or alcohol or illicit drug use disorders.

**TABLE 4. Multiple Regression of Withdrawal Symptoms on Psychiatric Disorders (N=239)**

| Disorder | B[a] | SE | p |
|---|---|---|---|
| Major depression | 0.875 | 0.334 | 0.009 |
| Any anxiety disorder | 0.842 | 0.289 | 0.004 |
| Alcohol abuse/dependence | 0.515 | 0.314 | 0.10 |
| Drug abuse/dependence | 0.095 | 0.332 | 0.78 |

[a] Partial unstandardized regression coefficient.

and decreased heart rate by 9.6%. Although symptoms not included in *DSM-III-R* were generally less common, they were not rare. For example, feeling depressed was reported by 22.6%, and tremor and headache were reported by 16.3% and 18%, respectively.

The mean number of withdrawal symptoms reported by smokers who had ever tried unsuccessfully to quit or cut down was 3.9 (SD=1.9). Heavy smokers, that is, persons who smoked more than 20 cigarettes daily, reported more withdrawal symptoms than light smokers: 4.5 (SD=1.9) and 3.5 (SD=1.8), respectively (t=4.006, df=237, p=0.0001). Table 2 shows the number of withdrawal symptoms—an indicator of severity of nicotine withdrawal— reported by the smokers who had tried to quit, according to sex, race, educational level, and marital status. Severity of nicotine withdrawal was unrelated to sex, educational level, or marital status (p>0.05). It was, however, greater in white persons than in black persons.

Smokers with histories of major depression, any anxiety disorder, or alcohol or illicit drug abuse/dependence reported, on the average, more symptoms after abstinence than smokers with no history of psychiatric disorders (table 3). Because of the high rates of co-occurrence among these disorders, we used multiple regression analysis to test and estimate the association of major depression and any anxiety disorder with severity of withdrawal, holding constant other disorders. The results appear in table 4, where ordinary least squares unstandardized partial regression coefficients are presented. As can be seen in table 4, a history of major depression and a history of any anxiety disorder were associated with more severe withdrawal. Specifically, each disorder, independent of the other disorder and of alcohol or illicit drug use disorders, was associated with an increase of nearly one withdrawal symptom. Alcohol and illicit drug abuse or dependence were unrelated to severity of withdrawal when major depression and any anxiety disorder were held constant. There were no significant two-way interactions among these variables, nor did the addition to the model of sex and of other psychiatric disorders ascertained in the study (specifically, mania and dysthymia) alter these results or enhance the prediction of withdrawal severity.

To examine whether there were specific symptom patterns, apart from more severe withdrawal overall, associated with a history of major depression or any anxiety disorder, we examined the prevalence of individual symptoms in persons with histories of major depression only, any anxiety disorder only, both disorders, and neither disorder (table 5). Compared to persons with neither of the two disorders, persons with histories of major depression only, but not those with histories of anxiety only or both disorders, reported higher frequencies of decreased heart rate and drowsiness. In addition, the rates of trouble concentrating and feeling depressed following attempts to quit were higher among persons who had histories of major depression than among any other subset of smokers. Per-

**TABLE 5. Relation Between Individual Withdrawal Symptoms and History of Major Depression and Anxiety Disorders in 239 Smokers Who Had Tried Unsuccessfully to Quit or Cut Down**

| | Neither Disorder (N=114) | | Major Depression Only (N=15) | | Anxiety Disorder Only (N=66) | | Both Disorders (N=44) | |
|---|---|---|---|---|---|---|---|---|
| Symptom | N | % | N | % | N | % | N | % |
| Craving for cigarettes | 89 | 78.1 | 13 | 86.7 | 53 | 80.3 | 41 | 93.2 |
| Irritability | 59 | 51.8 | 10 | 66.7 | 46 | 69.7 | 32 | 72.7 |
| Nervousness | 48 | 42.1 | 8 | 53.3 | 39 | 59.1 | 26 | 59.1 |
| Trouble concentrating | 24 | 21.0 | 6 | 40.0 | 20 | 30.0 | 15 | 34.1 |
| Restlessness | 55 | 48.2 | 8 | 53.3 | 38 | 57.6 | 35 | 79.6 |
| Decreased heart rate | 8 | 7.0 | 3 | 20.0 | 8 | 12.1 | 3 | 7.0 |
| Increased appetite | 68 | 59.6 | 8 | 53.3 | 38 | 57.6 | 29 | 65.9 |
| Headache | 14 | 12.3 | 2 | 13.3 | 15 | 22.7 | 12 | 27.3 |
| Drowsiness | 12 | 10.5 | 4 | 26.7 | 9 | 13.6 | 6 | 13.6 |
| Upset stomach | 6 | 5.3 | 1 | 6.7 | 6 | 9.1 | 8 | 18.2 |
| Tremor | 13 | 11.4 | 3 | 20.0 | 8 | 12.1 | 15 | 34.1 |
| Feeling depressed | 19 | 16.7 | 5 | 33.3 | 18 | 27.3 | 12 | 27.3 |

sons with histories of anxiety only or anxiety plus major depression reported higher rates of irritability, nervousness, and restlessness than smokers with histories of major depression only or smokers with neither anxiety nor major depression. Persons with histories of both anxiety and major depression had the highest rates of craving for cigarettes, increased appetite, headache, upset stomach, and tremor, in addition to irritability and restlessness.

Although the differences were not significant in multiple tests of each subset against each of the other subsets, the data suggest the possibility that patterns of withdrawal symptoms might vary among smokers with histories of major depression and those with anxiety only or anxiety and major depression. A history of major depression only might dispose toward dysphoria and depressive symptoms such as concentration problems and feeling unaroused, whereas a history of anxiety might dispose to nervousness and restlessness.

Of the total subset of 239 smokers who reported ever having tried unsuccessfully to quit or cut down, 206 had continued to smoke in the year preceding the interview; the remaining 33 had not. Table 6 shows results from a hierarchical logistic regression analysis, with continued versus discontinued smoking as the dependent variable. In the first regression, it can be seen that when any anxiety disorder was controlled, major depression was associated with continued smoking. The odds ratio for continued smoking was 3.22 (95% confidence interval=1.04–9.94), indicating that smokers with histories of major depression were more than three times as likely to have continued smoking as smokers with no history of major depression. Any anxiety disorder was unrelated to continued smoking when major depression was controlled. The addition of severity of withdrawal symptoms in the second regression did not reduce materially the association between a history of major depression and continued smoking, as can be seen from a comparison of the coefficients for major depression in the first and second regressions. Further, severity of withdrawal symptoms was unrelated to continued smoking according to these results. A comparison of the number of withdrawal symptoms of those who continued to smoke and those who did not yielded similar results. The mean number of withdrawal symptoms was 4.3 (SD=2.2) among those who continued to smoke and 4.1 (SD=2.3) among those who did not, a nonsignificant difference.

**TABLE 6. Hierarchical Multivariable Logistic Regression of Continued Smoking on Major Depression and Anxiety Disorders Before and After Introduction of Withdrawal Symptoms (N=239)**

| | Regression 1 | | | Regression 2 | | |
|---|---|---|---|---|---|---|
| Disorder | Logistic Odds | SE | p | Logistic Odds | SE | p |
| Major depression | 1.168 | 0.576 | 0.04 | 1.137 | 0.580 | 0.05 |
| Any anxiety disorder | –0.523 | 0.392 | 0.18 | –0.555 | 0.400 | 0.17 |
| Withdrawal symptoms | | | | 0.037 | 0.092 | 0.69 |

We also examined whether feeling depressed after quitting or cutting down accounted for the association between major depression and continued smoking, but we found no evidence of an intervening role for this disturbance or for the cluster of withdrawal symptoms that was reported more frequently by persons who had histories of major depression, namely, feeling depressed, trouble concentrating, decreased heart rate, and drowsiness.

## DISCUSSION

The key findings of this analysis were the following. 1) The rates of withdrawal symptoms varied between 82% (craving for cigarettes) and 8.8% (upset stomach). 2) Symptoms not included in *DSM-III-R*, although generally less common than *DSM-III-R* withdrawal symptoms, were not rare, ranging in prevalence from 22.6% (feeling depressed) to 8.8% (upset stomach). 3) Severity of nicotine dependence, defined by the total number of withdrawal symptoms, was higher in white than in black persons but was unrelated to sex, educational level, or marital status. 4) Persons with histories of major depression or any anxiety disorder reported more severe nicotine withdrawal than persons with neither major depression nor any anxiety disorder. 5) There was no strong evidence that a history of major depression or any anxiety disorder was associated with distinct patterns of withdrawal symptoms, although the data suggest some trends. 6) Severity of withdrawal was unrelated to the continuation of smoking and did not emerge as the mechanism that might explain the greater persistence of smoking by persons with histories of major depression.

The interpretation of these findings should take into account the nature of the epidemiologic data on which they are based. Information was elicited on nicotine withdrawal experienced at any time, rather than in close temporal proximity to its occurrence, as in studies of clinical samples. The accuracy of these reports might therefore have been influenced by differences in lag time among respondents. Nonetheless, several important strengths should be emphasized. This is the first general population study of nicotine withdrawal symptoms and their relationships with psychiatric disorders. Previous studies have reported more severe withdrawal and lower rates of quitting among smokers with dysphoric symptoms or major depression (7, 9–13, 15). Our study has the advantage of a comprehensive coverage of these widely distributed phenomena, which, until now, have been examined only in selected subsets of the population, chiefly smokers who have sought treatment in specialized medical settings.

With one exception, each of the seven symptoms listed for *DSM-III-R* nicotine withdrawal was reported more frequently than any of the non-*DSM-III-R* symptoms. The exception was decreased heart rate, with a prevalence of 9.6%. Of the subset of 239 smokers who had ever attempted unsuccessfully to quit or cut down, 50.2% (N=120) reported four or more *DSM-III-R* withdrawal symptoms and thus met the criteria for nicotine withdrawal. There are no comparable data on *DSM-III-R* nicotine withdrawal in general population samples. However, Hughes's estimate (16) of the rate of common withdrawal symptoms among smokers who quit on their own—50%—is equal to our observed rate of nicotine withdrawal. Both of these rates are lower than the 68% rate of *DSM-III-R* nicotine withdrawal reported for tobacco-dependent subjects recruited for a clinical trial (4). We found also that persons with histories of major depression and those with any anxiety disorder were more likely than those with neither of these disorders to meet the diagnostic criteria for nicotine withdrawal: 67.8%, 60.9%, and 37%, respectively.

The finding that a history of major depression was associated with more severe withdrawal is consistent with previous reports from clinical samples. In addition, we found that a history of any anxiety disorder, but not a history of alcohol or illicit drug abuse/dependence, was associated with more severe withdrawal. It should be noted that the significant associations with major depression and with any anxiety disorder were each observed independent of the other disorder as well as of coexisting alcohol or illicit drug abuse/dependence. Our results on the relation of major depression to continuation of smoking are in accord with previous reports that a history of depressive symptoms or major depression was associated with smoking and failure to quit (7, 9–12). However, the notion that severity of nicotine withdrawal or the presence of specific withdrawal symptoms, such as depressed mood, accounted for this association was unsupported. Moreover, severity of nicotine withdrawal and rates of individual withdrawal symptoms were unrelated to whether or not smokers (those with histories of major depression and those without) had continued to smoke in the year preceding the interview. It should be noted that in regard to the relation between severity of withdrawal and smoking cessation, previous studies have yielded conflicting results. Associations were reported in some but not all short-term follow-up studies (2–4, 6, 7). If discomfort from withdrawal could be expected to affect smoking behavior only in the short run, that is, 24 hours to 4 weeks, as has been suggested (2, 6), our finding of no association should come as no surprise, since we defined discontinued smoking as abstinence for at least 1 year prior to the interview.

Clearly, the elucidation of the effect of withdrawal symptoms on subsequent smoking behavior requires prospective studies, in which smokers are examined at specified intervals with respect to their quitting and smoking behavior. Although our finding that severity of withdrawal symptoms does not account for continued smoking must be viewed within the limitation of the study design, it suggests that prior experience of nicotine withdrawal has negligible long-term consequences for smoking behavior. This observation is consistent with the conclusions drawn recently from the available data on the process of quitting by oneself (17). According to the evidence, smokers who quit successfully have usually made numerous previous attempts. The number of previous attempts (despite its obvious relation to failed attempts) is unrelated to long-term success in quitting. Thus, even if severity of withdrawal symptoms had an immediate adverse effect on the outcome of a particular attempt to quit, it could not be expected to influence the final outcome of subsequent attempts. The dynamic process of quitting and the independence of withdrawal experiences from long-term smoking behavior might apply to all smokers, including those with histories of major depression, whose withdrawal disturbances are more severe. What, then, might account for the greater liability for persistent smoking in those with histories of major depression? Clinical psychopharmacology studies have reported euphoric, arousing, and antianxiety effects of smoking and nicotine (18–22). We suggest that the greater likelihood of continued smoking among smokers with histories of major depression might be explained by the greater positive reinforcing effects of smoking, chiefly, mood elevation and arousal, rather than the reinforcing effects of nicotine on the relief of withdrawal discomfort (2). To date, there is no empirical evidence bearing on this hypothesis, which clearly merits examination in future research.

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# Adrenergic Receptor Genes as Candidate Genes for Panic Disorder: A Linkage Study

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*Objective: Several lines of investigation suggest that the noradrenergic neurotransmitter system may be involved in the pathogenesis of panic disorder. Since a mutation in a gene coding for one of the adrenergic receptors could account for both the familial nature and autonomic dysfunction of panic disorder, the authors performed analyses of the linkage between panic disorder and five adrenergic receptor loci. Method: The subjects were 14 multiplex pedigrees with* DSM-III *panic disorder or agoraphobia with panic attacks. The loci tested were the* $\alpha_1/\beta_2$ *pair on chromosome 5q32-q34, the* $\alpha_2/\beta_1$ *pair on chromosome 10q24-q26, and a second* $\alpha_2$ *locus on chromosome 4. Flanking loci were included in the analysis on chromosomes 5 and 10 to increase the informativeness of the adrenergic receptor loci. Results: Lod scores less than –2.0 were found at all five receptor loci. Conclusions: These findings provide strong evidence against the possibility that genetic mutation at any of these loci is responsible for panic disorder in these pedigrees.*

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Noradrenergic dysfunction has been proposed as a mediating mechanism in anxiety and panic (1–4). The locus ceruleus and lateral tegmental noradrenergic afferents and efferents project to and from many areas of the brain that are thought to mediate the physiological and behavioral responses of fear (2, 5). In the monkey, stimulation of the locus ceruleus increases, and ablation reduces, fear-like behavior (6, 7). In humans, the noradrenergic system reaches maximal activity at the age when the incidence of panic disorder peaks (8). Many of the symptoms of panic attacks are suggestive of sympathetic nervous system excitation. Moreover, in patients with panic disorder, pharmacological stimulation of locus ceruleus outflow with yohimbine increases anxiety and norepinephrine turnover (9), and blocking of this outflow with clonidine reduces both (10). The tricyclic and monoamine oxidase inhibitor antidepressants may exert their antipanic effects by increasing available norepinephrine and by down-regulating postsynaptic noradrenergic receptors (11). The significantly lower density and greater affinity of lymphocyte β-adrenergic receptor binding sites (12) and the lower density of platelet $\alpha_2$-adrenergic receptor binding sites (13) in patients with panic disorder than in healthy subjects further implicate noradrenergic dysfunction in panic anxiety.

The actions of the noradrenergic system are mediated through two major classes of receptors, α and β. Two subtypes of each class (i.e., $\alpha_1$ and $\alpha_2$, $\beta_1$ and $\beta_2$) were initially classified on the basis of their pharmacologic properties (14). The $\alpha_2$, $\beta_1$, and $\beta_2$ receptors are coupled to the adenylate cyclase/cyclic AMP second messenger system. The $\beta_1$ and $\beta_2$ receptors stimulate adenylate cyclase and facilitate noradrenergic transmission, while $\alpha_2$ receptors act presynaptically to inhibit adenylate cyclase (14) and, through a major regulatory mechanism, reduce noradrenergic transmission (15). The $\alpha_1$ receptor acts through phospholipase C, primarily as a regulator of vascular tone (16). A recently identified $\beta_3$ receptor acts primarily to mediate the metabolic effects of catecholamines (17).

The adrenergic receptor genes are candidate genes for panic disorder because a genetic mutation could account for both the familial nature of panic disorder (18) and the evidence of noradrenergic dysfunction (1–4). This hypothesis can be tested by studying DNA probes for the adrenergic receptor genes as linkage markers in multiplex pedigrees of panic disorder. If the hypothesis is correct, it should be confirmed by a lod score supporting linkage, since genetic recombination between the disease and the gene responsible for it would not be expected to occur. Conversely, a negative lod score and the presence of obligate recombinants (i.e., affected individuals in the same family who do not share an allele at the candidate gene locus) would be strong evidence against the candidate gene hypothesis.

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DNA probes for five adrenergic receptor loci were included in the study: the $\alpha_1$ locus (*ADRA1*), an $\alpha_2$ locus on chromosome 10 (*ADRA2*) and one on chromosome 4 (*ADRA2L2*), $\beta_1$ (*ADRB1*), and $\beta_2$ (*ADRB2*). The $\alpha_1$ and $\beta_2$ loci map to chromosome 5q32-q34, where physical mapping places them 300 kilobases apart, and $\beta_1$ and an $\alpha_2$ locus map to chromosome 10q24-q26 within a 250-kilobase region (19).

DNA markers for four additional loci were included in the analyses: *D10S20* and *D10S27,* which flank the $\alpha_2$ and $\beta_1$ loci on chromosome 10 (20 and unpublished 1989 study by M.R. Hoehe et al.), and *D5S70* and *D5S36,* which flank the $\alpha_1$ and $\beta_2$ loci on chromosome 5 (20, 21, and personal communication from M.R. Hoehe). These loci were added to increase the informativeness of the adrenergic receptor probes on those two chromosomes. Not included in the study was a $\beta_3$ locus (17) and a third $\alpha_2$ locus on chromosome 2 (22). The action of the former is thought to be limited to the metabolic effects of catecholamines (17), and the latter is not expressed in brain (23); therefore, neither gene is a candidate for panic disorder.

## METHOD

### *Clinical Methods*

Fourteen pedigrees with panic disorder were ascertained on the basis of 1) a *DSM-III* diagnosis of panic disorder (N=2) or agoraphobia with panic attacks (N=12) in the proband, 2) at least three family members affected with panic disorder, definite or probable, or agoraphobia with panic attacks, and 3) unilateral disease transmission. The mean age of the 14 probands was 34.7 years (range=14–55), and 11 of the 14 were female. The mean age at onset was 23.4 years (range=8–35). These pedigrees have been reported on previously (24), but new family members have been added since that report.

Interviews were done by experienced clinicians (psychiatrists or senior residents) using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (25) for eight pedigrees and the Structured Clinical Interview for DSM-III (SCID) (26) for six. The structured interview was supplemented by a narrative summary and medical records when available. All of the subjects who were phenotyped and thus contributed to the lod scores of the linkage analyses were personally interviewed. Uninterviewed relatives who served as connecting links within the pedigrees were diagnosed through family history, as described elsewhere (24). These individuals did not contribute to the lod scores. Written informed consent was obtained from all participants.

Diagnoses were made by two of us (R.R.C. and R.N.) with *DSM-III* criteria after the interviews and narratives were reviewed, as described elsewhere (24). In addition, diagnoses of probable panic disorder were made for subjects who reported panic attacks but lacked a sufficient number of criterion symptoms or frequency of attacks to meet the criteria for a definite diagnosis. Similarly, diagnoses of probable agoraphobia were made for those with phobic symptoms but insufficient avoidance to meet the criteria for that diagnosis. All of the subjects with agoraphobia, definite and probable, had panic attacks. Clinical assessments were made blind to the genetic marker phenotypes.

We entered 186 individuals in the 14 pedigrees into the linkage analysis. DNA was typed for 154 pedigree members, 68 of whom were classified as affected: 21 with panic disorder (14 definite and seven probable) and 47 with agoraphobia with panic attacks (42 definite and five probable). Subjects who had the following additional primary diagnoses in the anxiety/affective disorders spectrum were coded as unaffected in the linkage analyses: major depression (N=8), alcohol abuse (N=8), substance use disorder (N=1), social phobia (N=2), obsessive-compulsive disorder (N=1), generalized anxiety disorder (N=1), atypical anxiety disorder (N=1), dysthymic disorder (N=1), and bipolar affective disorder (N=1).

### *Laboratory Methods*

DNA was extracted from buffy coats or lymphoblastoid cell lines by phenol-chloroform extraction and digested with restriction enzymes according to the recommendations of the manufacturer (Bethesda Research Labs, Inc., Bethesda, Md.). The digested samples were electrophoresed in 0.8% agarose gels in 1 X TPE (0.09 M Tris-phosphate, 0.002 M EDTA) and transferred to charged nylon membranes (Zetabind; AMF Cuno, Inc., Meriden, Conn.) according to the recommendations of the manufacturer. Probes were labelled with [$\alpha$-$^{32}$P]dCTP by using the random primer method and a commercial kit (Amersham, Inc., Arlington Heights, Ill.) and were hybridized with the membranes for 24 hours according to the recommendations of the manufacturer (AMF Cuno, Inc.). The membranes were washed with three 5-minute low-stringency washes (2 X standard saline citrate [SSC], 0.1% sodium dodecyl sulfate [SDS]) and one 20-minute high-stringency wash (0.1 X SSC, 0.1% SDS, 55 °C) and exposed to Kodak XAR-5 film (Eastman Kodak, Rochester, N.Y.) for 48 hours with image intensifier screens.

Five adrenergic receptor clones were provided by Dr. Robert Lefkowitz, Howard Hughes Medical Institute, Duke University Medical Center. The $\alpha_2$ chromosome 4 probe (pADRA2RL2) detects a two-allele *Bsu*36I RFLP (restriction fragment length polymorphism) (27), the $\alpha_2$ chromosome 10 probe (HPalpha2GEN) detects a two-allele *Dra*I RFLP (28), a $\beta_1$ clone (clone 11) detects a two-allele *Bgl*I RFLP (29), and the $\beta_2$ clone (pTF3) detects a two-allele *Ban*I RFLP (30). No RFLPs have been detected with the $\alpha_1$ clone (ARalpha).

Three of the four probes for the flanking loci were from the American Type Culture Collection, Rockville, Md. The *D5S70* probe (pTP5E) detects a two-allele *Taq*I RFLP; the *D5S36* probe (JO157E-A) detects a two-allele *Msp*I RFLP; the *D10S20* probe (OS-3) detects a three-allele *Taq*I RFLP, and the *D10S27* probe (cTBQ4, Howard Hughes Medical Institute, University

**TABLE 1. Lod Scores at Four Adrenergic Receptor Loci and Four Flanking Loci for 14 Pedigrees With Panic Attacks[a]**

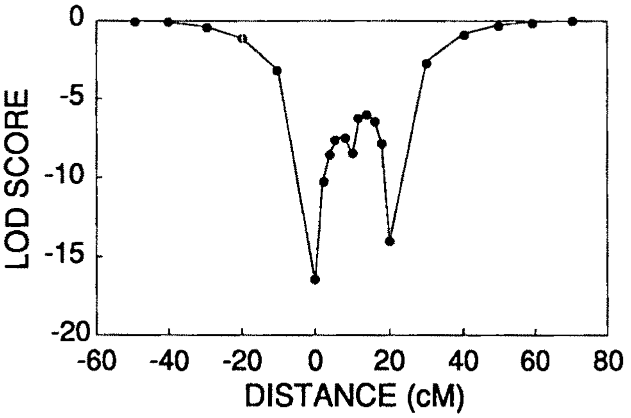
| | | Lod Score for Each Recombination Fraction | | | | | |
|---|---|---|---|---|---|---|---|
| Locus | Gene | 0.00 | 0.05 | 0.10 | 0.20 | 0.30 | 0.40 |
| *ADRA2L2* | $\alpha_2$[b] | –6.04 | –2.54 | –1.37 | –0.35 | –0.02 | 0.03 |
| *ADRA2* | $\alpha_2$[c] | –3.68 | –2.17 | –1.46 | –0.68 | –0.29 | –0.08 |
| *ADRB1* | $\beta_1$ | –0.65 | –0.47 | –0.33 | –0.15 | –0.06 | –0.01 |
| *ADRB2* | $\beta_2$ | –12.53 | –6.49 | –4.26 | –2.00 | –0.85 | –0.23 |
| *D10S20* | | –14.24 | –5.19 | –2.91 | –0.95 | –0.24 | –0.03 |
| *D10S27* | | –14.02 | –5.46 | –3.35 | –1.42 | –0.56 | –0.16 |
| *D5S70* | | –9.36 | –5.25 | –3.43 | –1.50 | –0.55 | –0.11 |
| *D5S36* | | –9.66 | –3.35 | –2.00 | –0.81 | –0.31 | –0.08 |

[a] Lod scores calculated with program LIPED (IBM PC/AT version, 1988). Genetic model included subjects with both definite and probable diagnoses of *DSM-III* panic disorder or agoraphobia with panic attacks and assumed a disease allele frequency of 0.014 and penetrance from 0 at age 10 increasing to a maximum of 0.80 at age 40 in females and half that at each respective age in males. The $\alpha_1$ locus is not polymorphic and does not appear here.

[b] Chromosome 4 locus.

[c] Chromosome 10 locus.

**FIGURE 1. Lod Scores for Linkage Between Panic Attacks and Three Loci on Chromosome 10q24-q26 in 14 Pedigrees[a]**



[a] The *D10S20* locus is arbitrarily set at 0 centimorgans (cM), $\alpha_2$ at 10 cM, and *D10S27* at 20 cM. Physical mapping data would place $\beta_1$ at approximately 10 cM. The genetic model included subjects with both definite and probable diagnoses of *DSM-III* panic disorder or agoraphobia with panic attacks and assumed a disease allele frequency of 0.014 and penetrance from 0 at age 10 increasing to a maximum of 0.80 at age 40 in females and half that at each respective age in males. The female-to-male recombination ratio is 2:1. The graph is a composite of two three-point analyses of panic disorder/agoraphobia with each successive pair of loci.

of Utah Medical Center) detects a two-allele *Msp*I RFLP. The DNA phenotypes were interpreted without knowledge of the diagnoses.

### *Statistical Methods*

Lod scores for linkage were computed with the program LIPED (IBM PC/AT version, 1988) for two-point analysis and the LINKMAP program of LINKAGE (version 5.04) for multipoint analysis. The female-to-male recombination ratio was set as 2:1 on chromosome 10 ($\alpha_2$ and $\beta_1$) and 5:1 on chromosome 5 ($\alpha_1$ and $\beta_2$) (20). The genetic model assumed an autosomal dominant disease allele with age- and sex-dependent penetrance and was informed by a segregation analysis of panic disorder in the Iowa population (31). Five variations of this model were tested.

Model 1 assumed subjects with both definite and probable cases of panic disorder or agoraphobia to be affected, a disease allele frequency of 0.014, and penetrance of 0 at age 10 increasing to a maximum of 0.80 at age 40 in females and half that at each respective age in males.

Model 2 used the same conditions as model 1 but included only definite cases of panic disorder and agoraphobia.

Models 3, 4, and 5 assumed the maximum penetrance to be 0.99, 0.60, and 0.01, respectively. These models, together with model 1, examined the effect of varying penetrance from 60% to 99% on the lod score to determine how robust the findings were to assumptions about penetrance. Model 5 based the lod score on affected individuals, eliminating assumptions about penetrance from the results.

## RESULTS

The results of the linkage analyses are presented in table 1 under genetic model 1. Since the adrenergic receptor loci were tested as candidate genes, the lod scores at the recombination fraction of 0.00 reflected the likelihood of linkage at each locus. The $\alpha_2$ locus on chromosome 4 resulted in a lod score of –6.04. The lod score at the $\alpha_2$ locus on chromosome 10 was –3.68. The $\beta_1$ locus was essentially uninformative, with a lod score of –0.65.

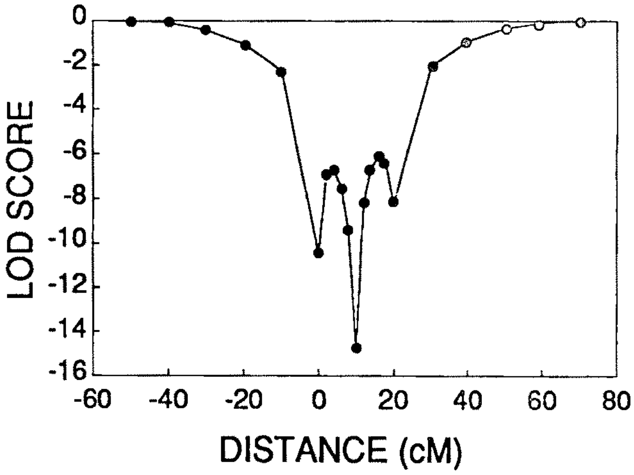
However, the $\beta_1$ locus is only 225 kilobases from the chromosome 10 $\alpha_2$ locus, and both loci lie between the *D10S20* and the *D10S27* loci. Therefore, multipoint analyses of these loci were performed to increase the informativeness of the $\beta_1$ locus. The two flanking markers were placed 20 centimorgans (cM) apart, and the $\alpha_2$/$\beta_1$ pair was arbitrarily set 10 cM from each flanking locus (20 and unpublished study by M.R. Hoehe et al.). The genetic model was model 1, and the female-to-male recombination ratio was assumed to be 2:1 (20). Figure 1 shows a lod score graph of two three-point analyses (panic disorder, *D10S20*, $\alpha_2$; and panic disorder, *D10S27*, $\alpha_2$). Lod scores less than –5.0 were obtained across the entire region in which the $\alpha_2$ and $\beta_1$ loci are located.

Similarly, a multipoint analysis was performed across the $\alpha_1$ and $\beta_2$ loci on chromosome 5 because the $\alpha_1$ clone is not informative for linkage. The $\alpha_1$ and $\beta_2$ loci are 300 kilobases apart and are flanked by the *D5S36* and *D5S70* loci, which lie 20 cM apart (20, 21). The $\beta_2$ locus is tightly linked to the probe cKK5.19 (M.R. Hoehe, personal communication), which lies between *D5S36* and *D5S70* (21). Therefore, we set *D5S36* and *D5S70* at 0 and 20 cM, respectively, and arbitrarily placed the $\alpha_1$ and $\beta_2$ loci at 10 cM on the map. Two three-point analyses were performed (panic disorder, *D5S36*, $\beta_2$; and panic disorder, *D5S70*, $\beta_2$). The genetic model was model 1, and the female-to-male recombination ratio was assumed to be 5:1 (20). The results are shown graphically in figure 2, and it can be seen that lod scores less than –6.0 were obtained across the entire region in which the $\alpha_1$ and $\beta_2$ loci are found.

The influence of assumptions about penetrance on the results was tested with four additional sets of analyses by varying penetrance from 0.01 to 0.99. All four resulted in negative lod scores at all four loci tested. The least informative model was the one that assumed a penetrance of 0.01, since this analysis discounted information on unaffected pedigree members. It resulted in the following lod scores at a recombination distance of 0.00: –2.53 at the $\alpha_2$ chromosome 4 locus, –2.18 at the $\alpha_2$ chromosome 10 locus, –6.77 at the $\beta_2$ locus, and –0.59 at the $\beta_1$ locus. The last analysis considered only subjects with definite diagnoses of panic disorder or agoraphobia as affected and classified subjects with probable diagnoses as unaffected. Lod scores at the four respective loci were –4.57, –2.86, –10.10, and –0.67. With the flanking markers, lod scores less than –2.0 were obtained at all four loci in both sets of analyses. These results indicate that the lod scores obtained in the primary analysis were not dependent on assumptions about clinical phenotype or gene penetrance.

The data were not tested for heterogeneity because there was no evidence of it on inspection of the lod scores by pedigree. At the $\alpha_2$ and $\beta_1$ loci on chromosome 10 all informative lod scores were negative. At the $\alpha_2$ locus on chromosome 4 one pedigree had a lod score of +0.76 and two had lod scores of +0.15. At the $\beta_2$ and $\alpha_1$ loci on chromosome 5 one pedigree had a lod score of +0.25. While linkage cannot be excluded in these pedigrees, lod scores of this magnitude are well within the bounds of chance.

**FIGURE 2. Lod Scores for Linkage Between Panic Attacks and Three Loci on Chromosome 5q32-q34 in 14 Pedigrees**[a]



[a]The *D5S36* locus is arbitrarily set at 0 centimorgans (cM), $\beta_2$ at 10 cM, and *D5S70* at 20 cM. Physical mapping data would place $\alpha_1$ at approximately 10 cM. The genetic model included subjects with both definite and probable diagnoses of *DSM-III* panic disorder or agoraphobia with panic attacks and assumed a disease allele frequency of 0.014 and penetrance from 0 at age 10 increasing to a maximum of 0.80 at age 40 in females and half that at each respective age in males. The female-to-male recombination ratio is 5:1. The graph is a composite of two three-point analyses of panic disorder/agoraphobia with each successive pair of loci.

## DISCUSSION

We found strong evidence against linkage between panic disorder and any of the five adrenergic receptor loci tested. This conclusion holds true regardless of whether panic disorder is defined broadly, to include borderline cases, or narrowly, to include only definite diagnoses. The findings also remain valid across a variety of genetic models, varying penetrance from 0.01 to 0.99. Obligate recombinants, i.e., two or more affected individuals in the same family who share neither allele at the candidate gene locus, were noted at all three informative loci: $\alpha_2$ on chromosome 10, $\alpha_2$ on chromosome 4, and $\beta_2$. Since these individuals were all affected, the apparent recombination could not have resulted from incorrect classification due to incomplete penetrance. While obligate recombinants constitute strong evidence against linkage to a candidate gene, this evidence rests on the assumption that only one disease allele is segregating in each pedigree.

While the results argue against mutation of any of these adrenergic receptors as a cause of panic disorder, several considerations should be kept in mind when interpreting the results in light of the noradrenergic hypothesis of panic disorder. Receptors represent only one link in the chain of neurotransmission. Defects in cell signaling occurring before the receptor or in second messenger systems after the receptor could still be at fault. Up- or down-regulation of receptors resulting from differences in gene expression could also be involved in the modulation of anxiety, and such abnormalities in gene regulation would not be detectable through linkage.

Another consideration is the broad heterogeneity of receptor subtypes in the CNS (32). In addition to the five adrenergic receptor loci tested, a $\beta_3$ receptor has been reported (17), as well as an additional $\alpha_2$ sequence on chromosome 2 (22). While neither of these genes appears to be a reasonable candidate for mediating behavior, other receptor subtypes that are candidates may yet be identified.

A third consideration is the possibility that panic disorder is etiologically heterogeneous. If a genetic mutation in an adrenergic receptor gene were a rare cause of panic disorder, this would be difficult to detect by linkage because the detection of linkage typically requires pooling data across pedigrees. For this reason the lod scores from the individual pedigrees at each locus tested were examined, and no evidence of linkage in any pedigree was found.

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# Comorbidity of Parental Anxiety Disorders as Risk for Childhood-Onset Anxiety in Inhibited Children

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*Objective: Previous work suggested that children of parents with panic disorder and agoraphobia were likely to be classified as behaviorally inhibited and that behaviorally inhibited children were likely to develop anxiety disorders. However, the factors determining which inhibited children were at risk for childhood onset of anxiety disorders remained unknown. The authors of this study hypothesized that greater anxiety loading in parents would increase the risk for anxiety disorders in children with behavioral inhibition. Method: Using* DSM-III *structured interviews, the authors examined patterns of aggregation of anxiety disorders in parents of two existing cohorts of children, one cross-sectional and clinically derived (31 children, 60 parents) and the other epidemiologically derived and longitudinal (40 children, 75 parents). Within each cohort, parents were stratified into three groups based on the presence (behavioral inhibition and anxiety) or absence (behavioral inhibition only, no behavioral inhibition and no anxiety) of behavioral inhibition and two or more anxiety disorders in their child. Results: Parents of children with behavioral inhibition and anxiety, from both the clinical and nonclinical cohorts, had significantly higher rates of two or more anxiety disorders than did parents of children with behavioral inhibition only and parents of children with no behavioral inhibition and no anxiety. Conclusions: These results indicate that the presence of parental loading for anxiety disorders may help to identify the subgroup of inhibited children at very high risk for developing childhood-onset anxiety disorders.*

(Am J Psychiatry 1992; 149:475–481)

In a recent report from the Institute of Medicine (1), the identification of early risk factors for childhood psychopathology was deemed a high priority for psychiatry research. One potential risk factor is temperamental differences among young children. A well-characterized temperamental construct is that termed by Jerome Kagan and colleagues of the Harvard Infant Study Laboratory as "behavioral inhibition to the unfamiliar" (2, 3). This laboratory-based temperamental construct is characterized by the consistent tendency to display fear and withdrawal in situations that are novel or unfamiliar (4). Behavioral inhibition can be identified at an early age; for example, in a recent report (5), behavioral inhibition at 14 months of age was predicted by responses to stimuli in children as young as 4 months of age.

Rosenbaum et al. (6) previously reported high rates of behavioral inhibition in young children of parents with panic disorder and agoraphobia. Further (7), they found that parents of behaviorally inhibited children from a nonclinical cohort studied by Kagan et al. (4) were also at greater risk for anxiety disorders, mainly social phobia. Biederman et al. (8) reported that children of parents with panic disorder and agoraphobia were also at greater risk for childhood anxiety disorders. These findings, taken together, are consistent with the literature implicating family-genetic risk factors in the development of anxiety disorders (9–17). Biederman et al. (18) showed that the risk for pathological anxiety, particularly when strictly defined by the presence of two or more anxiety disorders in the child, fell exclusively among those with behavioral inhibition and not among those without behavioral inhibition (20% versus 0%), regardless of whether the children were from a clinical or nonclinical population. Overall, these findings point to behavioral inhibition as a reflection of

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the familial risk for anxiety, but the factors that determine the development of anxiety disorders in inhibited children require further investigation.

We reasoned that if inhibited children who already manifest anxiety disorders have a more severe anxiety diathesis, they may have greater familial loading for anxiety risk factors than those who manifest behavioral inhibition alone. Following a model of familial transmission proposed by Reich (19, 20), a more severe phenotype (i.e., behavioral inhibition and anxiety disorders) would require more familial etiological factors for its expression than would the less severe form (i.e., behavioral inhibition alone). Since anxiety disorders tend to manifest themselves concomitantly, greater familial loading for anxiety disorders could express itself as two or more anxiety disorders in the parents. Thus, it is plausible that inhibited children with anxiety disorders will have greater loading for an anxiety diathesis, manifested by the presence of two or more anxiety disorders in the parents, than will children with behavioral inhibition alone. This research question remains unanswered.

## METHOD

We examined patterns of childhood- and adult-onset psychiatric disorders in parents of two independently ascertained, previously described, and preexisting cohorts of children. One cohort was cross-sectional and clinically derived (a general hospital at-risk cohort) (18), and the other was epidemiologically derived and longitudinal (Kagan et al. longitudinal cohort) (18). Detailed methodology of the ascertainment of the groups has been described in earlier reports (4, 6–8, 18). All parents signed informed consent forms for participation in this study.

### *At-Risk Cohort*

The at-risk group consisted of children (2 to 7 years) of outpatient parents with panic disorder and agoraphobia treated at the department of psychiatry of a general hospital and children with relatives without panic disorder and agoraphobia treated at the same outpatient clinic. Only those children who were assessed for behavioral inhibition and who were old enough to be assessed for psychopathology (4 years or older) (index children: N=31, parents: N=60) are included in this analysis. Before the assessment of behavioral inhibition, these eligible children were matched for age, socioeconomic status, and ordinal position with the comparison group of children who had relatives with other psychiatric disorders.

Assessments of behavioral inhibition were conducted at a university infant study laboratory. The evaluation consisted of a series of age-appropriate cognitive tasks following protocols that had been developed and used in other studies of behavioral inhibition (2, 4, 21–23). These protocols were designed to obtain an index of each child's behavior with an unfamiliar examiner under mild cognitive stress. The observations of the protocol sessions were videotaped and scored by coders who had no knowledge of parental diagnosis. On the basis of these observations, children were dichotomized into two mutually exclusive categories, inhibited and not inhibited. Children were assigned to the inhibited and not inhibited groups by an investigator who was blind to the assessment of psychopathology in the children and in their parents.

### *Longitudinal Cohort*

The longitudinal cohort is a well-described (2, 4, 21–23), preexisting cohort consisting of 40 index children between the ages of 7 and 8 years at the time of the assessment of psychopathology (parents: N=75). These children had been selected originally at age 21 months from a larger group of 305 Caucasian children born in local hospitals whose mothers, responding to questions in a telephone interview, had described their children as tending to be either inhibited (manifesting withdrawal) or uninhibited (displaying approach) in a range of situations. On the basis of these interviews, 117 children came to a laboratory where their behavior was observed and quantified in a variety of unfamiliar settings. The children who consistently displayed the major behavioral signs of inhibition (i.e., long latencies to interact with unfamiliar adults and cessation of play or vocalization), as well as those who consistently did not, were selected to form groups of the most inhibited (inhibited) and the most uninhibited (uninhibited) children. Each group represented about 10% to 15% of the original cohort. The children we assessed were all of those who had been studied longitudinally through the age of 7.5 years by Kagan and colleagues since their initial assessment and assignment to the inhibited and uninhibited groups at 21 months. We did not have access to those children who did not continue to be studied longitudinally.

### *Assessment of Psychopathology*

As described in earlier reports (6–8, 18), all children 4 years of age and older were assessed by interviews with the mothers that used the Diagnostic Interview for Children and Adolescents, Parent Version (24–26), a structured instrument that is based on diagnostic criteria from *DSM-III*. Rated *DSM-III* childhood anxiety disorders were separation anxiety disorder, overanxious disorder, avoidant disorder, and phobic disorders.

Assessments of parents were based on direct interviews that used the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (27) to assess anxiety disorders (panic disorder, agoraphobia, social phobia, simple phobia, and obsessive-compulsive disorder) and major depressive disorder. An addition from the Diagnostic Interview for Children and Adolescents (24) was included to assess past childhood anxiety diagnoses (separation anxiety disorder, overanxious disorder, and avoidant disorder) in the parents.

All interviews were conducted by specially trained raters with graduate or undergraduate degrees in psychology and with established interrater reliability (overall kappa=0.88, SD=0.04). The training consisted of familiarization with the study design and objectives, psychiatric nosology of *DSM-III,* and the structured interviews used (the Diagnostic Interview for Children and Adolescents, Parent Version, and the DIS). Raters in training first observed interviews carried out by experienced raters and clinicians and subsequently conducted at least two interviews while being observed by senior raters before they started to rate subjects independently. Raters were supervised by the two senior investigators (J.F.R. and J.B.). Interviews were audiotaped for random review and reliability assessments. Raters were blind to the temperamental classification of the children and final diagnoses of the parents. Raters were not blind to ascertainment site. Before final diagnostic assignment, all diagnostic information was reviewed by the first two authors, who also were blind to the temperamental classification of the children. Only definite diagnoses were used to determine rates of disorders. Rates of disorders presented reflect lifetime prevalences.

Since meeting criteria for a single anxiety disorder in a structured interview that assesses multiple disorders may sacrifice specificity for sensitivity and thus may not reflect serious and clinically applicable psychopathology, and since the anxiety disorders tend to occur concomitantly (28, 29), we have previously proposed that a more clinically meaningful variable would be defined by the presence of two or more concomitant anxiety disorders, termed multiple anxiety disorders (6–8, 18). Thus, in parents we assessed multiple anxiety disorders (in adult or childhood), multiple adult anxiety disorders, and multiple childhood anxiety disorders, and in children we assessed multiple childhood anxiety disorders. We also examined the presence of multiple anxiety disorders in parents from a developmental perspective as expressed by the manifestation of a childhood-onset anxiety disorder followed by an adult-onset anxiety disorder in the same person, termed continuing anxiety disorder.

### *Data Analysis*

Data were analyzed separately for each ascertainment group (at-risk cohort and longitudinal cohort). At each site, we stratified children into the following three groups on the basis of the presence or absence of behavioral inhibition and multiple (two or more) anxiety disorders (hereafter termed anxiety): 1) behavioral inhibition and anxiety, 2) behavioral inhibition only, and 3) no behavioral inhibition and no anxiety. There were no children in either cohort who were not inhibited and who met criteria for multiple anxiety disorders (anxiety only).

Statistical analyses were made among groups within each ascertainment cohort (at-risk cohort and the longitudinal cohort). For categorical data, 3×2 chi-square comparisons were made, followed by 2×2 comparisons using Fisher's exact test. For overall group comparisons involving continuous data, the nonparametric Kruskal-Wallis analysis was used. In cases where this overall comparison was significant, the Mann-Whitney U test was used for pairwise comparisons among groups. All analyses were two-tailed, and results were considered statistically significant if the p value was less than 0.05.

**TABLE 1. Hypothesized Risk for Anxiety Disorders and Behavioral Inhibition in Children of Parents With Multiple[a] Anxiety Disorders**

| | Hypothesized Risk in Children[b] | | |
|---|---|---|---|
| Parental History of Multiple[a] Anxiety Disorders | Behavioral Inhibition and Multiple[a] Anxiety Disorders | Behavioral Inhibition Only[c] | Neither |
| Any | ++ | + | — |
| Childhood | ++ | + | — |
| Adult | ++ | + | — |
| Childhood and adult | ++ | + | — |

[a] Two or more.

[b] ++=Very high risk, +=high risk, —=low risk.

[c] No multiple anxiety disorders.

### *Study Hypothesis*

We predicted that behaviorally inhibited children with anxiety would have greater loading than behaviorally inhibited children without anxiety for an anxiety diathesis, manifested by the presence of multiple anxiety disorders in the parents (table 1). Accordingly, we also expected parents of children with behavioral inhibition but no early onset of anxiety to be at intermediate risk between those with behavioral inhibition and anxiety and those with neither behavioral inhibition nor anxiety.

## RESULTS

### *At-Risk Cohort*

The sociodemographic characteristics of the parents and children in this cohort are displayed in table 2. There were no significant differences in age or sex among the children in each of the three groups. In addition, there were no differences in age, socioeconomic status, sex, and marital status among the parents of these three groups.

Three-way comparisons among parents of children with behavioral inhibition and anxiety, behavioral inhibition only, and no behavioral inhibition and no anxiety revealed statistically significant differences in the rates of two or more anxiety disorders (87.5% versus 32.1% versus 20.8%; $\chi^2$=11.91, df=2, p=0.003), two or more adulthood anxiety disorders (75.0% versus 28.6% versus 8.3%; $\chi^2$=13.74, df=2, p=0.001) (table 3), panic disorder with agoraphobia (75.0% versus 28.6% versus 12.5%; $\chi^2$=10.91, df=2, p=0.004), and the comorbid condition of panic disorder and agoraphobia with major depressive disorder (50.0% versus 10.7% versus 12.5%; $\chi^2$=7.41, df=2, p=0.025). Follow-up pairwise comparisons revealed that these findings were accounted for by the higher

**TABLE 2. Demographic Characteristics of Children at Risk for Anxiety Disorders, Children in Longitudinal Cohort, and Their Parents**

| | Number | | Age (years) | | | | Number of Each Sex | | | | Socio-economic Status[a] | | Parents Married | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Parents | | Children | | Parents | | Children | | | | | |
| Disorders in Children | Parents | Index Children | Mean | SD | Mean | SD | M | F | M | F | Mean | SD | N | % |
| At-risk cohort | | | | | | | | | | | | | | |
| Behavioral inhibition and multiple[b] anxiety disorders | 8 | 4 | 35.4 | 4.9 | 5.5 | 0.6 | 4 | 4 | 2 | 2 | 2.8 | 1.2 | 4 | 50.0 |
| Behavioral inhibition only[c] | 28 | 15 | 37.0 | 8.4 | 5.5 | 1.1 | 14 | 14 | 9 | 6 | 2.8 | 1.3 | 20 | 71.4 |
| Neither | 24 | 12 | 37.3 | 5.7 | 4.7 | 0.8 | 12 | 12 | 6 | 6 | 2.6 | 1.1 | 18 | 75.0 |
| Longitudinal cohort | | | | | | | | | | | | | | |
| Behavioral inhibition and multiple[b] anxiety disorders | 8 | 4 | 38.6 | 2.5 | 7.9 | 0.2 | 4 | 4 | 1 | 3 | 2.5[d] | 0.5 | 6 | 75.0 |
| Behavioral inhibition only[c] | 32 | 18 | 40.4 | 5.2 | 7.9 | 0.2 | 17 | 15 | 6 | 12 | 1.7 | 0.7 | 31 | 96.9 |
| Neither | 35 | 18 | 38.9 | 6.4 | 7.9 | 0.2 | 18 | 17 | 9 | 9 | 2.1 | 0.9 | 31 | 88.6 |

[a] Significant difference within the longitudinal cohort (H=6.48, df=2, p=0.04, Kruskal-Wallis test).
[b] Two or more.
[c] No multiple anxiety disorders.
[d] Significantly different from the same cohort group with no behavioral inhibition or multiple anxiety disorders (U=56, Z=–2.44, p=0.02, Mann-Whitney U test).

**TABLE 3. History of Multiple[a] Anxiety Disorders in Parents of Children at Risk for Anxiety Disorders and Parents of Children in Longitudinal Cohort**

| | History of Multiple[a] Anxiety Disorders in Parents | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Any[b] | | Childhood[c] | | Adult[d] | | Childhood and Adult[c] | |
| Disorders in Children | N | % | N | % | N | % | N | % |
| At-risk cohort | | | | | | | | |
| Behavioral inhibition and multiple[a] anxiety disorders | 7 | 87.5[e] | 1 | 12.5 | 6 | 75.0[e] | 3 | 37.5 |
| Behavioral inhibition only[f] | 9 | 32.1 | 5 | 17.9 | 8 | 28.6 | 7 | 25.0 |
| Neither | 5 | 20.8 | 2 | 8.3 | 2 | 8.3 | 2 | 8.3 |
| Longitudinal cohort | | | | | | | | |
| Behavioral inhibition and multiple[a] anxiety disorders | 4 | 50.0[g] | 3 | 37.5[g] | 2 | 25.0 | 3 | 37.5[g] |
| Behavioral inhibition only[f] | 6 | 18.8 | 3 | 9.4 | 1 | 3.1 | 6 | 18.8 |
| Neither | 3 | 8.6 | 1 | 2.9 | 1 | 2.9 | 2 | 5.7 |

[a] Two or more.
[b] Significant difference between cohorts (longitudinal: $\chi^2$=7.88, at risk: $\chi^2$=11.91, df=2, p<0.05).
[c] Significant difference within the longitudinal sample ($\chi^2$=9.24, df=2, p<0.05).
[d] Significant difference between cohorts (longitudinal: $\chi^2$=6.86, at risk: $\chi^2$=13.73, df=2, p<0.05).
[e] Significantly different from two other groups in the cohort (p<0.05, Fisher's exact test).
[f] No multiple anxiety disorders.
[g] Significantly different from same cohort group with no behavioral inhibition or multiple anxiety disorders (p<0.05, Fisher's exact test).

rate of these disorders in the parents of children with behavioral inhibition and anxiety than in the parents of children with behavioral inhibition only and no behavioral inhibition and no anxiety. Although parents of the children with behavioral inhibition only had substantially (1.5 to 3.5 times) higher rates of all multiple anxiety disorders than the parents of the children with no behavioral inhibition and no anxiety, these differences failed to attain statistical significance. The differences among the groups appear to be specific to anxiety disorders, since the rates of major depressive disorder did not differ among the three groups (50.0% versus 39.3% versus 33.3%; p>0.05).

### *Longitudinal Cohort*

The sociodemographic characteristics of the parents and children in this cohort are displayed in table 2. There were no significant differences in age or sex among the children in each of the three groups. Although there were small but statistically significant differences for socioeconomic status in parents, there were also no differences in age, sex, or marital status among the three groups of parents. The difference in socioeconomic status was accounted for by the higher socioeconomic status in the behavioral inhibition and anxiety group than in the group with behavioral inhibition only.

Three-way comparisons among parents of children with behavioral inhibition and anxiety, behavioral inhibition only, and no behavioral inhibition and no anxiety revealed statistically significant differences in the rates of two or more anxiety disorders (50.0% versus 18.8% versus 8.6%; $\chi^2$=7.88, df=2, p=0.02), two or more childhood anxiety disorders (37.5% versus 9.4% versus 2.9%; $\chi^2$=9.24, df=2, p=0.009), two or more adulthood anxiety disorders (25.0% versus 3.1% versus 2.9%; $\chi^2$=6.86,

**TABLE 4. History of Multiple[a] Anxiety Disorders in Parents of Pooled Cohorts of Children at Risk for Anxiety Disorders and Children in Longitudinal Cohort**

| | History of Multiple[a] Anxiety Disorders in Parents | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Any[b] | | Childhood | | Adult[c] | | Childhood and Adult[d] | |
| Disorders in Children | N | % | N | % | N | % | N | % |
| Behavioral inhibition and multiple[a] anxiety disorders | 11 | 68.8[e] | 4 | 25.0[f] | 8 | 50.0[e] | 6 | 37.5[f] |
| Behavioral inhibition only[g] | 15 | 25.0 | 8 | 13.3 | 9 | 15.0 | 13 | 21.7[f] |
| Neither | 8 | 13.6 | 3 | 5.1 | 3 | 5.1 | 4 | 6.8 |

[a] Two or more.
[b] Significant difference among groups ($\chi^2$=8.72, df=2, p<0.05).
[c] Significant difference among groups ($\chi^2$=21.78, df=2, p<0.05).
[d] Significant difference among groups ($\chi^2$=10.04, df=2, p<0.05).
[e] Significantly different from other two groups (p<0.05, Fisher's exact test).
[f] Significantly different from group with no behavioral inhibition or multiple anxiety disorders (p<0.05, Fisher's exact test).
[g] No multiple anxiety disorders.

df=2, p=0.03), continuing anxiety disorder (37.5% versus 18.8% versus 5.7%; $\chi^2$=6.00, df=2, p=0.05) (table 3), social phobia (50.0% versus 9.4% versus 0%; $\chi^2$=19.24, df=2, p<0.001), and the comorbid condition of social phobia and major depressive disorder (12.5% versus 0% versus 0%; $\chi^2$=8.49, df=2, p=0.02). Follow-up pairwise comparisons revealed that these findings were accounted for by the higher rate of these disorders in the parents of children with behavioral inhibition and anxiety than in the parents of children with behavioral inhibition only and/or no behavioral inhibition and no anxiety. As in the at-risk cohort, although parents of the children with behavioral inhibition only had substantially (2.2 to 3.2 times) higher rates of all multiple anxiety disorders than parents of children with no behavioral inhibition and no anxiety, these differences failed to attain statistical significance. The differences among the groups appear to be specific to the anxiety disorders, since the rate of major depressive disorder did not differ among the three groups (12.5% versus 18.8% versus 14.3%, p>0.05).

### *Exploratory Data Analysis*

Because of the similarities in the findings in both cohorts, and despite methodologic limitations to such an approach, an exploratory analysis of pooled data from both cohorts was conducted to obtain an overview of the findings with improved power (table 4). With enhanced statistical power, the pooled data comparing behavioral inhibition only to no behavioral inhibition and no anxiety were statistically significant. In the pooled cohort, the rates of social phobia (10.0% versus 0%; p=0.01, Fisher's exact test) and continuing anxiety disorder (21.7% versus 6.8%; p=0.03, Fisher's exact test) were statistically higher in parents of children with behavioral inhibition only than in parents of children with no behavioral inhibition and no anxiety.

## DISCUSSION

We have previously hypothesized that the presence of behavioral inhibition in a child may be a marker or precursor of risk for development of an anxiety disorder in childhood, adulthood, or both. Previous work suggested that young children of parents with panic disorder and agoraphobia were likely to be classified as behaviorally inhibited (6) and that behaviorally inhibited children from both clinical and nonclinical cohorts were likely to develop anxiety disorders (18). While parental panic disorder and possibly social phobia are associated with behavioral inhibition in offspring (6, 7) and while behavioral inhibition is associated with a greater risk for childhood anxiety disorders (18), the factors determining which inhibited children were at risk for childhood onset of anxiety disorders were unknown. The findings reported here indicate that the inhibited children whose anxiety disorders were reported by their mothers were those with the greatest familial loading for anxiety disorders, manifested in the form of multiple anxiety disorders in the parent. These results support the hypothesis that behavioral inhibition and anxiety may be a more severe form of an "anxiety-prone" diathesis. These findings appear to be specific for anxiety disorders, since the rate of major depressive disorder did not differ among the groups.

While our hypothesis predicts that differences in parental anxiety disorders should be found in the comparisons between the groups with behavioral inhibition only and no behavioral inhibition and no anxiety (table 1), that could not be statistically established because of limited statistical power. However, in both the at-risk and longitudinal cohorts, although the rates of grouped anxiety disorders (table 3) in the group with behavioral inhibition only were 1.5 to 3.5 times higher than those in the group with no behavioral inhibition and no anxiety, these differences failed to attain statistical significance. Although tentative in nature, results of the exploratory analysis of pooled findings did reveal statistically significant differences between the groups with behavioral inhibition only and no behavioral inhibition and no anxiety groups for continuing anxiety disorder and social phobia, as well as a trend for two or more adult anxiety disorders (p=0.07). These pooled data more clearly illustrate a progression in the risk for anxiety disorders in parents of children with no behavioral inhibition and no anxiety, behavioral inhibition only, and behavioral inhibition and anxiety. These findings suggest that while the presence of behavioral inhibition in a child may be a risk factor in the development of anxiety disorders, their manifestation is more likely in the presence of high familial loading, expressed as multiple anxiety disorders in the parent.

There are likely to be multiple factors influencing the development of manifest anxiety disorders in children with behavioral inhibition, including, for example, adverse environmental influences in general and the specific interaction of inhibited temperament with developmental adversity. The latter may include exposure to a parent with greater psychopathology.

For example, Eisenberg, observing separation anxiety in young children, suggested that the perception by the child of dependency needs (and anxiety) in the mother accounted for the inability to separate and attend school (avoidant behavior) (30). Moreover, agoraphobic parents have been described as either overprotective or unavailable to the child, thereby interfering with the normative process of separation and individuation.

While our findings cannot discern the relative importance of genetically versus environmentally transmitted risk factors, the recognition of parental risk factors in inhibited children enhances early identification of children at greatest risk and the possibility of developing early interventions to minimize the progression of psychopathology and associated distress and impairment.

The findings in this study should be viewed in light of their methodologic limitations. The cohort sizes of individual subgroups were relatively small to evaluate fully the nature of the association between behavioral inhibition and anxiety disorders. Despite limited power, significant differences in the expected direction were found. While the small cohort size reduces the precision of our estimates of rates of disorders and the power to detect differences, only a robust finding should have achieved significance in a small cohort.

Since psychometric data are available only for rating children 6 years or older, another concern is that the assessment of psychopathology in children younger than 6 years may be less certain than that of older children; nonetheless, we elected to include children younger than 6 years since the purpose of this pilot study was to obtain psychopathological data on as many children as possible. As has been recently reviewed by Weissman (29), a lower age limit of 4 years has been used for assessments of children in other high-risk and epidemiologic studies (31).

The assessment of psychopathology in the children was based on interviews with the mothers, which may have led to ascertainment bias and misrepresentation of psychopathology in the children. However, the same method was used to evaluate all groups of children. Some parents were known to have psychiatric disorders, and this may have affected the reported rates of childhood symptoms, since psychiatric patients may exaggerate symptoms in their children (32); alternatively, normal mothers may have a tendency to underreport problem behaviors (33). Nevertheless, high rates of anxiety disorders, similar to those found in the at-risk cohort, were found in the longitudinal cohort in which ascertainment of behavioral inhibition was not based on parental psychopathology (18).

In summary, our results indicate that while children of parents with anxiety disorders have a greater risk for manifesting behavioral inhibition, parental loading for anxiety disorders may account for the early onset of anxiety syndromes in these children. If confirmed, this finding may help identify the subgroup of inhibited children at very high risk for developing childhood-onset anxiety disorders.

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# Antisocial Behavior of Intravenous Drug Abusers: Implications for Diagnosis of Antisocial Personality Disorder

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*Objective: A pattern of chronic adult antisocial behavior is not sufficient for the* DSM-III-R *diagnosis of antisocial personality disorder unless the early-onset criteria are satisfied, even if the adult criteria are met. The utility of the early-onset requirement for the diagnosis was examined in intravenous drug abusers, a population known to have high rates of irresponsible, aggressive, and criminal behavior. Method: The subjects were 237 drug abusers who had volunteered for an outpatient study of psychopathology and HIV risk behavior and infection. They completed a structured psychiatric interview as part of their participation in that study. The adult antisocial behavior of the group that met both the early-onset and the adult criteria for antisocial personality disorder, the group that met only the adult criteria, and the group that met neither the early-onset nor the adult criteria was then compared. Results: Antisocial personality disorder (meeting the early-onset and adult criteria) was diagnosed in 44% of the sample; an additional 24% met only the adult criteria. The group with the diagnosis of antisocial personality disorder reported a more pervasive and more serious pattern of adult antisocial behavior than did the other groups, although antisocial behavior was commonplace in all three groups. Conclusions: Early onset of multiple antisocial behaviors identified a subset of drug abusers with important differences in the extent and severity of their adult antisocial behavior. The antisocial behavior of the group that met only the adult criteria suggests the possibility of a late-onset and less severe form of antisocial personality disorder.*

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Antisocial behavior is strongly linked to drug abuse (1–3). Ball et al. (3) interviewed 354 drug abusers regarding their day-to-day criminal activities. All subjects reported a history of adult antisocial behavior, including the illegal sale of drugs, illegal gambling, theft, and other criminal offenses. Despite the fact that adult antisocial behavior is commonplace among drug abusers, previous research indicates that most of these persons fail to satisfy the diagnostic criteria for antisocial personality disorder. For example, the prevalence of this disorder in drug abusers when the *DSM-III* (or *DSM-III-R*) definition is used has ranged from 35% (4) to a high of 54% (5), with an average prevalence rate of about 40% (6, 7).

What accounts for the fact that most drug abusers fail to meet the diagnostic criteria for antisocial personality disorder? One potential explanation may be related to how *DSM-III* and *DSM-III-R* operationalize the disorder. Each of these systems uses definitions with a strong behavioral framework that require early onset (before the age of 15) of multiple antisocial behaviors for a patient to become eligible for the adult diagnosis. Thus, to be classified as having antisocial personality disorder, a person must have fulfilled at least three of 12 specific antisocial criteria (e.g., truancy, chronic lying, aggressiveness, and criminality) prior to the age of 15 and fulfill at least four of the adult criteria (e.g., unstable work history, chronic lying, aggressiveness, criminality). As a result of the requirement for early onset, persons with high rates of adult antisocial behavior (including those who may satisfy the adult criteria for antisocial personality disorder) would not be diagnosed as having the disorder unless they also meet the early-onset criteria.

This aspect of the current definition of the disorder has been criticized by Hare (8) and was discussed recently in a review by Gerstley et al. (6). These criticisms

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raise important questions about the clinical utility of the early-onset requirement for the diagnosis of antisocial personality disorder, particularly for drug abusers, who typically report high rates of adult criminality, aggressiveness, irresponsibility, and unemployment. To examine this issue further, we compared the rates of specific adult antisocial behaviors among intravenous drug abusers to determine whether there were meaningful differences between those who satisfied both the early-onset and adult criteria for antisocial personality disorder, those who satisfied the adult criteria but not the early-onset criteria, and those who satisfied neither the adult nor the early-onset requirements for the disorder.

## METHOD

The 237 subjects presented in this report were intravenous drug abusers participating in a longitudinal study of psychopathology and HIV high-risk drug use and sexual behavior. The sample included subjects who were in a hospital-based methadone treatment program (N=128) and subjects who were not in methadone treatment at the time of enrollment in the study (community sample, N=109). All subjects who were in treatment met the *DSM-III-R* criteria for current opioid dependence, and many also had at least one additional substance use disorder, primarily related to cocaine use (68%, N=87). These subjects had been in methadone treatment for at least 3 months and had been recruited by advertisements posted in the treatment clinic. Community subjects were eligible for inclusion in the study if they reported intravenous drug use within the 3 months before study enrollment, had a lifetime history of intravenous drug abuse for more than 3 continuous months, and had less than 12 months of cumulative methadone treatment in the 4 years before entering the study. Nearly all of the community subjects satisfied current diagnostic criteria for an opioid (N=89) and cocaine (N=104) use disorder. They were recruited by advertisements in selected health and research agencies and by chain-referral techniques. Each subject was paid $10 per hour for completing the intake assessment instruments, for a total of approximately 6 hours ($60). Informed consent was obtained from each subject after study procedures were fully described. Given the sensitive nature of these data, a confidentiality certificate was obtained for the project from the National Institute on Drug Abuse, which would protect the data from subpoena.

The mean age of the subjects was 36.0 years (SD=6.6, range=23–63); 70% (N=165) were male. Forty percent (N=95) of the subjects were white, 59% (N=140) were black, and less than 1% (N=2) were Hispanic or Native American. The mean educational level was 11.0 years (SD=1.9, range=5–19); 67% (N=159) were unemployed. Forty-six percent (N=109) had never married, 14% (N=33) were married, 35% (N=83) were separated/divorced, and 5% (N=12) were widowed. They reported onset of recurring life problems associated with any substance use at a mean age of 18.8 years (SD=4.9, range=11–45) and an average of 33.2 months (SD=50.0, range=0–240) of cumulative (lifetime) methadone maintenance. Subjects who were in treatment were more likely to be white (66%, N=84, versus 9%, N=10; $\chi^2=76.05$, df=1, $p<0.001$) and married (19%, N=24, versus 6%, N=7; $\chi^2=7.58$, df=1, $p<0.01$). More of the community subjects were male (83%, N=90, versus 59%, N=75; $\chi^2=14.89$, df=1, $p<0.001$).

The diagnoses of antisocial personality and substance use disorders followed *DSM-III-R* guidelines and were made from a modified version of the Alcohol Research Center Intake Interview, a semistructured diagnostic interview with good reliability and procedural validity (9). This interview was derived from both the Schedule for Affective Disorders and Schizophrenia—Lifetime version (10) and the National Institute of Mental Health Diagnostic Interview Schedule (11). The Alcohol Research Center Intake Interview covers the major substance use disorders (excluding nicotine and caffeine) and other psychiatric conditions most prevalent among alcohol and drug abusers (e.g., major depression and antisocial personality disorder), including several categories with low prevalence but high morbidity (e.g., schizophrenia and bipolar disorder).

All interviews were conducted by trained research interviewers with master's degrees in social work or clinical/counseling psychology. Clinical interviewers were required to complete a minimum of 4 hours of didactic training on the interview, to rate a minimum of five consecutive interviews that agreed with an expert interviewer's diagnostic ratings of the subject, and then to conduct a minimum of five subject interviews that agreed with the ratings of an expert interviewer.

The data concerning specific behaviors before and after the age of 15 were derived from items in the demographic and antisocial personality sections of the diagnostic interview. All subjects were interviewed on each of these items, with continuous measures formatted to provide quantitative data on the frequencies of these behaviors. Illegal activities (and formal charges) directly involving drugs and alcohol (e.g., possession and sale of illicit drugs, driving while intoxicated, public intoxication) were not included in the number of misdemeanors or felonies reported by subjects, although no attempt was made to exclude behaviors that may have been motivated by drug abuse (e.g., chronic lying, prostitution, theft, assault). In addition, subjects were compared on a summary measure of more serious adult criminality and physically aggressive behavior that was constructed from a subset of the interview questions. This composite measure of severe antisocial behavior was derived by calculating the sum of the number of times since the age of 15 that subjects had used weapons in fights, been arrested for felonies, and committed felonies that did not result in arrest.

Demographic and treatment history variables for the group that met neither the early-onset nor the adult criteria for antisocial personality disorder, the group that met the adult criteria only, and the group that met both

**TABLE 1. Childhood and Adult Antisocial Behaviors Reported by Intravenous Drug Abusers Divided Into Three Groups According to Fulfillment of the *DSM-III-R* Criteria for Antisocial Personality Disorder**

| | Both[a] (N=104) (B) | | Adult Only[b] (N=56) (A) | | Neither[c] (N=60) (N) | | Significant Post Hoc Comparisons (p<0.05) |
|---|---|---|---|---|---|---|---|
| Variable | N | % | N | % | N | % | |
| Before age 15 (early onset) | | | | | | | |
| Truancy | 70 | 67.6 | 12 | 21.4 | 12 | 20.0 | B>A,N |
| Suspensions | 81 | 77.9 | 18 | 32.1 | 13 | 21.7 | B>A,N |
| Incorrigibility | 40 | 38.7 | 4 | 7.3 | 4 | 6.7 | B>A,N |
| Running away | 48 | 46.2 | 5 | 8.9 | 1 | 1.7 | B>A,N |
| Chronic lying | 76 | 73.1 | 9 | 16.1 | 7 | 11.7 | B>A,N |
| Multiple sex partners | 34 | 32.4 | 1 | 1.8 | 6 | 10.0 | B>A,N |
| Destruction of property | 37 | 35.3 | 2 | 3.6 | 1 | 1.7 | B>A,N |
| Setting fires | 18 | 17.3 | 3 | 5.4 | 0 | 0.0 | B>A,N |
| Use of weapons | 32 | 30.7 | 1 | 1.8 | 0 | 0.0 | B>A,N |
| Instigating fights | 41 | 39.0 | 3 | 5.4 | 2 | 3.3 | B>A,N |
| Arrests | 49 | 47.1 | 7 | 12.5 | 4 | 6.7 | B>A,N |
| Other illegal acts | 70 | 67.0 | 14 | 25.0 | 4 | 6.7 | B>A>N |
| Reform school | 35 | 34.0 | 4 | 7.1 | 1 | 1.7 | B>A,N |
| After age 15 (adult) | | | | | | | |
| Current unemployment | 77 | 74.0 | 40 | 71.4 | 36 | 60.0 | |
| Chronic unemployment | 89 | 85.4 | 49 | 87.5 | 30 | 50.8 | B,A>N |
| Problems with monogamy | 19 | 18.3 | 9 | 16.1 | 1 | 1.7 | B,A>N |
| Chronic lying | 91 | 87.5 | 40 | 71.4 | 21 | 35.0 | B>A>N |
| Homelessness | 52 | 50.0 | 22 | 39.3 | 4 | 6.7 | B,A>N |
| Use of weapons | 59 | 56.4 | 21 | 37.5 | 4 | 6.7 | B>A>N |
| Misdemeanor arrests | 61 | 58.7 | 37 | 66.1 | 19 | 31.7 | B,A>N |
| Other misdemeanors | 85 | 82.0 | 34 | 61.5 | 16 | 27.1 | B>A>N |
| Felony arrests | 75 | 71.8 | 25 | 45.5 | 17 | 28.3 | B>A,N |
| Other felonies | 75 | 71.8 | 25 | 44.6 | 6 | 10.0 | B>A>N |

[a] Subjects meeting both the early-onset and the adult criteria for antisocial personality disorder.
[b] Subjects meeting only the adult criteria for antisocial personality disorder.
[c] Subjects meeting neither the early-onset nor the adult criteria for antisocial personality disorder.

sets of criteria were compared by analysis of variance or chi-square tests. Analyses of the percentages of subjects who had engaged in the various childhood and adult antisocial behaviors were done by means of chi-square tests (with continuity correction) with post hoc testing of group differences by the Tukey-Kramer method. The frequencies of specific childhood and adult antisocial behaviors were compared for the three groups by means of analysis of covariance and Tukey's post hoc test; age at onset of recurring life problems associated with drug use was used as a covariate because groups were significantly different on this variable. While it would have also been appropriate to include gender as a grouping factor in this analysis, the resulting cell sizes would have been too small for meaningful interpretation of the results. All analyses were conducted with the SPSS (12), and results were considered significant if the p value was less than 0.05.

## RESULTS

Of the 237 subjects, 44% (N=104) were classified as having antisocial personality disorder, since they met both the early-onset and the adult criteria (Both), 24% (N=56) met only the adult criteria (Adult Only), and 25% (N=60) satisfied neither the early-onset nor the adult criteria (Neither). An additional 7% (N=17) met the early-onset requirement but failed to meet the adult criteria for the disorder. This last group was too small to permit meaningful statistical comparisons and was omitted from the analyses. Thus, all statistical comparisons were made between subjects in the three remaining groups (N=220).

More of the subjects in the Both and the Adult Only groups than in the Neither group were male (79.8%, 71.4%, and 51.7%, respectively; $\chi^2$=14.42, df=2, p=0.001), and more of the subjects in the Neither group than in the Both and the Adult Only groups were married (21.7%, 9.6%, and 5.4%, respectively; $\chi^2$=8.31, df=2, p=0.02). Those in the Both group also reported a significantly earlier age at onset of recurring life problems associated with substance use than those in the Adult Only and the Neither groups (17.4, 20.1, and 20.7 years, respectively; F=10.99, df=2, 215, p<0.001). There were no significant differences between the three groups on age, ethnicity, years of education, employment status, cumulative (lifetime months) of methadone treatment, or methadone treatment status (treatment or no treatment) at the time of study enrollment.

The patterns of antisocial behavior in the three groups were evaluated in two ways: first, by comparing the percentages of subjects reporting any involvement in each of the behaviors, and second, where possible, by comparing their frequencies of occurrence.

Table 1 shows the percentages of subjects in the three groups who reported prior involvement in each of the childhood and adult antisocial behaviors covered by the

**TABLE 2. Results of Analyses of Covariance on Frequencies of Antisocial Behaviors Among Intravenous Drug Abusers Divided Into Three Groups According to Fulfillment of the *DSM-III-R* Criteria for Antisocial Personality Disorder**

| Variable | Both[a] (N=104) (B) | | Adult Only[b] (N=56) (A) | | Neither[c] (N=60) (N) | | Significant Post Hoc Comparisons (p<0.05) |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| Before age 15 (early onset) | | | | | | | |
| Truancy | 4.49 | 5.20 | 1.21 | 3.36 | 0.57 | 1.33 | B>A,N |
| Suspensions | 3.19 | 4.97 | 0.55 | 1.22 | 0.32 | 0.68 | B>A,N |
| Incorrigibility | 5.44 | 10.64 | 0.64 | 2.37 | 0.75 | 3.35 | B>A,N |
| Running away | 1.28 | 2.65 | 0.11 | 0.37 | 0.10 | 0.77 | B>A,N |
| Multiple sex partners | 2.55 | 5.22 | 0.05 | 0.40 | 0.38 | 1.22 | B>A,N |
| Destruction of property | 3.73 | 8.92 | 0.13 | 0.72 | 0.02 | 0.13 | B>A,N |
| Reform school | 0.51 | 0.93 | 0.07 | 0.26 | 0.02 | 0.13 | B>A,N |
| Setting fires | 0.58 | 1.62 | 0.05 | 0.23 | 0.00 | 0.00 | B>A,N |
| Use of weapons | 2.38 | 6.56 | 0.11 | 0.80 | 0.00 | 0.00 | B>A,N |
| Instigating fights | 4.38 | 9.52 | 0.52 | 2.80 | 0.12 | 0.78 | B>A,N |
| Arrests | 1.40 | 2.98 | 0.18 | 0.51 | 0.07 | 0.25 | B>A,N |
| Other illegal acts | 24.03 | 45.17 | 4.98 | 21.04 | 2.12 | 13.25 | B>A,N |
| After age 15 (adult) | | | | | | | |
| Different employers | 10.18 | 8.43 | 10.13 | 8.27 | 7.17 | 5.59 | B>N |
| Years of monogamy | 4.39 | 3.46 | 6.45 | 5.09 | 7.65 | 4.05 | B<A,N |
| Use of weapons | 4.45 | 6.43 | 3.27 | 8.70 | 0.20 | 0.90 | B,A>N |
| Misdemeanor arrests | 3.61 | 7.59 | 2.84 | 6.21 | 0.50 | 0.91 | B>N |
| Other misdemeanors | 50.23 | 89.19 | 42.69 | 92.87 | 10.10 | 26.88 | B>N |
| Felony arrests | 3.73 | 4.37 | 1.84 | 3.26 | 0.57 | 1.08 | B>A,N |
| Other felonies | 40.51 | 92.12 | 15.11 | 42.44 | 1.60 | 7.32 | B>N |

[a] Subjects meeting both the early-onset and the adult criteria for antisocial personality disorder.
[b] Subjects meeting only the adult criteria for antisocial personality disorder.
[c] Subjects meeting neither the early-onset nor the adult criteria for antisocial personality disorder.

interview. As expected, significantly more of the subjects in the Both group than in the Adult Only and Neither groups had been involved in each of the childhood behaviors, including having been placed in reform school. There were no significant differences between the percentages of subjects in the Adult Only and the Neither groups who had been involved in these early life behaviors, with the exception that more of the Adult Only group had engaged in "other illegal acts."

On measures of adult antisocial behavior, there were also consistent differences between the Both and the Neither groups (table 1). With the exception of current unemployment, a greater percentage of subjects in the Both group had been involved in each of the adult behaviors. In contrast, comparisons between subjects in the Both and the Adult Only groups yielded mixed results. Similar percentages of subjects in the Both and the Adult Only groups reported employment problems, difficulty maintaining a monogamous relationship, homelessness, and misdemeanor arrests. However, compared to the Both group, significantly fewer subjects in the Adult Only group had been arrested for a felony, committed a felony not resulting in arrest, committed a misdemeanor not resulting in arrest, used weapons in fights, or developed a pattern of chronic lying. It is interesting that significantly more subjects in the Adult Only group than in the Neither group had been involved in each of the adult behaviors, with the exception of felony arrest and of unemployment at the time of study entry. In short, subjects in the Adult Only group appeared to be behaviorally different from and intermediate between those in the Both and the Neither groups.

Table 2 shows the comparison of the three groups with respect to the number of times subjects reported committing specific antisocial acts. These comparisons were restricted to those questions which provided data on the number of times a specific behavior occurred (e.g., number of times arrested, number of times weapons were used in fights). As would be expected, the group with antisocial personality disorder (Both) reported significantly higher frequencies on each of the measures of childhood antisocial behavior than did the Adult Only and the Neither groups. Importantly, the Adult Only and Neither groups did not differ significantly on the frequency of any of these early life behaviors.

The relationships were notably different with respect to the adult behavior of these groups. Although the Both group reported uniformly higher frequencies than the Neither group on all of the antisocial behaviors (including fewer years of monogamy), comparisons between the Both and the Adult Only groups produced more variable results. In general, the antisocial behavior of the Adult Only group was intermediate between that of the Both and Neither groups and most often did not differ significantly from that of either group. Compared to the Both group, the Adult Only group reported a significantly lower number of felony arrests ($q=4.69$, $df=3, 216$, $p=0.01$) and felonies not resulting in arrest ($q=3.23$, $df=3, 216$, $p=0.05$) and more continuous years of monogamy ($q=4.30$, $df=3, 216$, $p=0.01$). In contrast, the two groups did not differ significantly on number of misdemeanor arrests, misdemeanors not resulting in arrest, or number of different employers since the age of 18 years.

Although subjects in the Adult Only group were more likely than the Neither group to be involved in most measures of adult antisocial behavior (table 1), they did not typically differ from each other in the frequencies of these behaviors (table 2). The one exception to this general finding was that subjects in the Adult Only group used weapons more frequently in fights than did those in the Neither group (q=3.73, df=3, 216, p=0.05).

Finally, the three groups were compared on the previously described summary measure of severe criminality and physical aggressiveness. The Both group obtained a significantly higher mean score (48.13) than that of the Adult Only group (20.18) (q=3.47, df=3, 216, $p<0.05$) and that of the Neither group (2.37) (q=5.81, df=3, 216, $p<0.01$). Perhaps more important, the mean score for the Adult Only group was not significantly different from that for the Neither group (q=1.97, df=3, 216, n.s.).

## DISCUSSION

It is interesting that many drug abusers fail to satisfy requirements for the *DSM-III* (and *DSM-III-R*) definition of antisocial personality despite their high rate of antisocial behavior. In this study only 44% of the subjects were classified as having antisocial personality disorder even though most reported chronic adult antisocial problems. Importantly, 42% (N=56) of those not diagnosed as having antisocial personality disorder met the adult criteria for the disorder. Although there were some similarities in adult antisocial behavior across the three groups, the general conclusion drawn from this study is that the early-onset requirement for the diagnosis of antisocial personality disorder is important. For the subjects who met this diagnostic requirement, adult antisocial behavior was more probable and more frequent than for subjects who did not. This relationship is shown most clearly in the comparison of the group of adult intravenous drug abusers who fulfilled both the early-onset and the adult criteria with the group who fulfilled neither set of criteria. There, within a population that was homogeneous with respect to involvement in an antisocial adult lifestyle (intravenous drug abuse), drug abusers diagnosed as having antisocial personality disorder displayed significantly more pervasive and more severe adult antisocial behavior. The relationship is also seen, though less strongly, in the comparison of the group that fulfilled both sets of criteria with the group that fulfilled only the adult criteria. There, the populations compared were even more homogeneous, all engaging in sufficient numbers and frequencies of antisocial behaviors to satisfy the requirements for adult antisocial personality disorder. Still, the various adult antisocial behaviors assessed were more likely to occur, and the composite severity index of these behaviors was higher, for those who met the full criteria for the disorder by having also engaged in multiple chronic antisocial behaviors prior to age 15.

While the adult antisocial behavior of the group who fulfilled both sets of criteria was more pervasive and more frequent than that of the group who met only the adult criteria, subjects in the latter group did report high levels of adult antisocial behavior. This finding raises several possibilities. First, the subjects who met only the adult criteria may constitute a subset of antisocial patients with late onset and a less severe form of the disorder who simply avoided many of the problems measured by the early-life criteria. Second, the high rate of antisocial behavior reported by this group may be associated with their chronic drug abuse. This is partially supported by the fact that even subjects in the group that fulfilled neither set of criteria had histories of recurring adult antisocial behavior, including chronic unemployment, criminal misdemeanors, and felony arrests. It is relatively well established that antisocial behavior is a frequent consequence of drug abuse (13, 14). In the present study, the subjects who fulfilled the adult criteria only and the subjects who fulfilled neither set of criteria had onset of recurring life problems associated with their use of drugs at about 20 years of age. The onset of problem drug use in these subjects was concurrent with their self-reported increase in pervasive antisocial behavior. The severe antisocial lifestyle of the group diagnosed as having antisocial personality disorder may also have been exacerbated by their chronic drug abuse (13, 14).

At minimum, these data supporting the importance of the early-onset requirement in the diagnosis of antisocial personality disorder confirm previous studies reporting a strong association between multiple antisocial behaviors early in life and more severe adult antisocial problems (15, 16). In addition, the greater extent and severity of adult antisocial problems reported by the group with antisocial personality disorder may also be associated with previous findings on a subset (N=100) of these patients that strongly linked antisocial personality disorder to higher rates of HIV high-risk drug use behaviors (7) and with other studies reporting that the disorder is often associated with poor drug abuse treatment outcome (17, 18).

There are several caveats associated with this study. Data were obtained by self-report without the benefit of additional informants or arrest records. However, Maisto et al. (19) found that drug abusers typically provide valid information about illegal and drug use activities when no contingencies (positive or negative) are associated with their reports. Also, Zimmerman et al. (20) reported that the use of other informants did not improve the diagnosis of antisocial personality disorder made on the basis of subjects' self-reports.

Another concern is that approximately 50% of the subjects in our study were not in treatment at the time they completed the interview. The fact that they were not in treatment may have resulted in higher rates of adult antisocial behavior. However, there were no significant differences in the numbers of treatment and community subjects in each of the three subject groups. Further, there were no significant differences between groups in the numbers of cumulative lifetime months of methadone treatment. The demographic and drug use characteristics (i.e., intravenous opioid and cocaine use) of the sample may restrict generalizability of these data to other intravenous narcotic and cocaine abusers demographically similar to those in the present study.

Finally, the study was limited to a retrospective examination of group differences on a restricted range of antisocial behaviors. The inclusion of other measures of personality and antisocial behavior in the study could have provided a more comprehensive view of the differences between the group that met the criteria for antisocial personality disorder and the group that met the adult criteria only. Such work is currently underway at this center with another sample of drug abusers newly admitted to an outpatient drug treatment program.

## CONCLUSIONS

The clinical utility of the *DSM-III-R* early-onset criteria in the definition of antisocial personality disorder represents an important issue in the diagnosis of this disorder. This issue may be especially important in the assessment of drug abusers, given the potential of classifying most as having the disorder if the early-onset requirement is ignored. The present study supported the importance of an early onset of pervasive antisocial behaviors for the diagnosis of antisocial personality disorder in drug abusers. The current definition of antisocial personality disorder, including the early-onset requirement, clearly does not detect all individuals who will engage in extensive antisocial behavior as adults, as shown by the behavior of the Adult Only group. However, the data from this study indicate that adult intravenous drug abusers who do meet the early-onset criteria are, on average, more deviant and more impaired.

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# Sensory Gating Deficits in Schizophrenia: New Results

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*Objective: It has been widely hypothesized that sensory gating failures and sensory overload occur in schizophrenic patients compared to normal subjects. The authors of this study sought to confirm and extend results of earlier studies that showed specific sensory gating deficits in schizophrenic patients. Method: Age- and sex-matched schizophrenic patients (N=20) and normal subjects (N=20) were tested using electrophysiologically recorded P50 event-related potentials to assess the overall competence of the subjects' central sensory inhibitory capacity by measuring sensory filtering or gating. P50 area responses to two 75-dB (conditioning and test) click stimuli of 0.04-msec duration, averaged over 60 trials, were recorded for each subject. Normally, the first (conditioning) click stimulus induces gating mechanisms that result in diminished or gated P50 event-related potentials in response to the second click stimulus. Results: The schizophrenic subjects manifested a significant sensory gating deficit at frontal, central, and parietal electrode placement sites, with a nonsignificant tendency for the deficit to be most prominent in the frontal areas of the brain. Conclusions: These data reflect a regionally diffuse loss of normal sensory gating in schizophrenic patients.*

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Since the time of Kraepelin and Bleuler, abnormalities of attention and information processing have been identified among patients with diagnoses in the schizophrenic spectrum of disorders. In recent years, investigators have used information-processing paradigms in studies of both humans and animals to specify the time course of information-processing deficits and the possible underlying neuroanatomical and neurophysiological abnormalities that evoke these deficits (1). Earlier, McGhie and Chapman (2) discussed "disorders of attention and perception in early schizophrenia" and noted that organisms integrate sensory data by utilizing a buffer capacity that allows for perceptual constancy by reduction of the "otherwise chaotic flow of information reaching consciousness." This is very similar to Venables' view (3) that in some schizophrenic individuals there is stimulus "flooding" through sensory overload based on a failure of normal filtering and gating mechanisms. Still, theories of sensory gating abnormalities in schizophrenia are often confusing and difficult to operationalize. This led Neale and Cromwell (4) to call for "refined behavioral techniques utilizing relevant behavioral cues" in gating studies.

In more recent years, a number of investigators have used innovative techniques to specify the sensory gating deficits and corresponding sensory overload and inundation that occur in some schizophrenic spectrum patients. Gottschalk et al. (5) used a novel paradigm to illustrate that sensory overload (or LSD treatment) could induce changes in normal subjects' scores on social alienation-personal disorganization and cognitive-intellectual impairment scales that are similar to the test results of schizophrenic patients. Specifically, Gottschalk et al. subjected normal control subjects to sensory overload by using an "overload apparatus" that consisted of a geodesic dome into which cacophonous sounds and fragmenting, bizarre, and complex visual images were projected. The results were consistent with sensory gating deficit theories, since cognitive fragmentation occurred when individuals experienced sensory overload.

Other studies of sensory overload and sensory gating deficits in patients with schizophrenic disorders have been reported in which cortically based event-related potentials were used. Braff et al. (6) used a self-stimulation paradigm in which the subject uses a key release to initiate a stimulus that elicits event-related potentials. The P300 wave component of event-related potentials reflects the amount of novel or unanticipated informa-

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tion delivered by a stimulus. Thus, the P300 component is diminished when the subject has elicited the stimulus (in contrast to a randomly generated stimulus), and this diminution is greatest at brief intervals (e.g., 100 msec) between key release and stimulus onset, when the subject is aware that the stimulus is about to "arrive." Schizophrenic subjects, however, show a paradoxically decreased P300 amplitude in the 250–500-msec interval, indicating a diminution of the normal inhibitory mechanisms that operate in this time frame.

In a related series of studies, Freedman, Adler, Siegel, and associates found that medicated (7) and unmedicated (8) schizophrenic patients, as well as relatives of schizophrenic patients (9), showed deficits in a sensory gating study in which a two-stimulus (conditioning and test) event-related potentials paradigm was used. Both of the stimuli used in this paradigm evoke P50 waves that occur in the epoch about 50 msec after stimulus onset. The second stimulus usually evokes a P50 wave that is inhibited or gated by the effect of the first stimulus. Schizophrenic patients exhibit a lack of this normal inhibitory influence and thus show a larger than normal P50 wave elicited by the second stimulus that could reflect a deficit in sensory gating. This deficit is not an artifact of antipsychotic medications, since unmedicated schizophrenic patients and family members of schizophrenic patients show similar deficits. Kathmann and Engel (10) reported that this loss of P50 gating in schizophrenic patients was not reproduced in their study. It is noteworthy, however, that the click stimulus they used in their study was many times more powerful than that used by Freedman and associates because of its longer duration (1.5 msec versus 0.04 msec). In related work with animals, Adler et al. (11) proposed that these deficits are caused by a state of hyperarousal, with hyperexcitable neurons causing a defect in normal cortical and subcortical inhibitory mechanisms. The existence of this viable animal model allows for novel and enlightening studies of the mechanisms underlying gating failures in schizophrenic patients.

Since their initial reports (7, 8), there has not been independent confirmation in another laboratory of Freedman and associates' observations of sensory gating deficits in schizophrenic patients compared with normal or patient control subjects. The only report from another laboratory (10) failed to confirm Freedman and associates' basic finding. Our study was designed to use the P50 event-related potentials paradigm to replicate and extend Freedman and associates' findings of sensory gating deficits in schizophrenic patients.

## METHOD

The subjects were 20 medicated schizophrenic patients recruited from the inpatient psychiatry service of a university medical center. The patients were between 18 and 55 years of age and met the *DSM-III* criteria for schizophrenia. In addition, the patients were administered the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (12), and patients meeting the Research Diagnostic Criteria (RDC) (13) for schizophrenia were included in the study. The Brief Psychiatric Rating Scale (14) and the Global Assessment Scale (15) were also administered to all patients.

The mean age of the schizophrenic patients (15 male and five female) was 28.8 years (SD=8.49, range=18–53 years). Their average dose of antipsychotic medications was 1996 mg/day of chlorpromazine equivalents. Eighteen of the patients were right-handed and two were left-handed. Potential subjects who had current or recent histories of alcoholism, drug abuse, dementia, or ECT were excluded, as in our previous method (16).

Twenty normal subjects (14 male and six female) with no active psychopathology or family history of schizophrenia were recruited from advertisements in local papers and from among the medical center staff. All were administered the SADS-L. Only subjects who were medically healthy and met the RDC for "never mentally ill" were included in the normal group. The mean age for this group was 27.9 years (SD=5.99, range=18–39 years). Seventeen of these subjects were right-handed and three were left-handed.

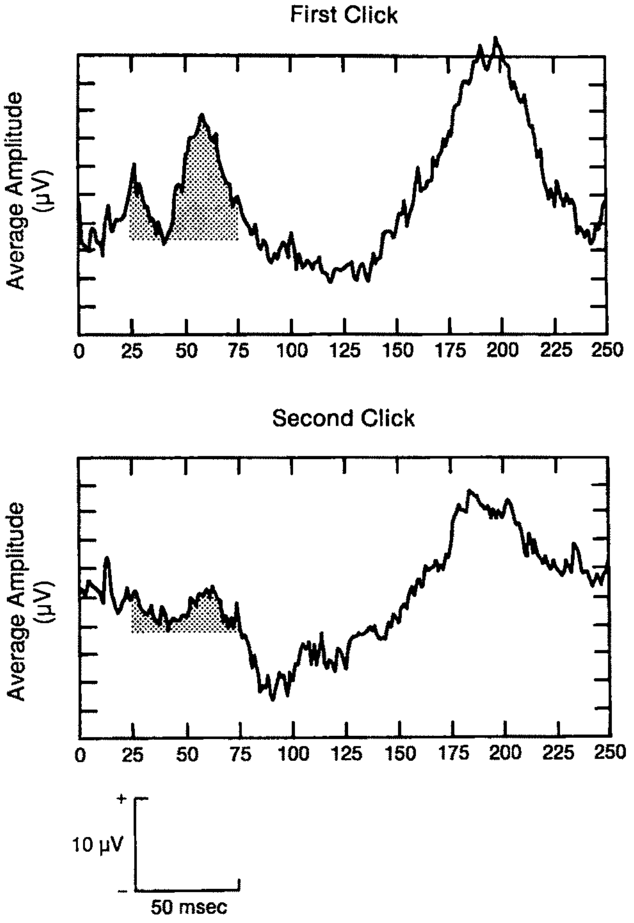
Informed consent was obtained from all subjects.

All recordings were performed in the electrophysiology laboratory of one of us (L.L.J.) in a shielded chamber with a DEC-MINC computer and Grass amplifiers. Recordings were made from gold cup electrodes (resistances less than 5 Ω) placed at the midline frontal, central, and parietal sites according to the 10/20 system. Electrodes were referenced to linked ear electrodes. In general, the recording methods closely followed those published by Freedman and associates (7–9), so that the results would be comparable to their published data. One difference, however, was that we used 60 pairs of stimuli in these experiments, whereas Adler et al. (7) used 32 pairs.

Electrical activity was amplified 20,000 times by a 1-MΩ impedance amplifier with band pass filters (–3 dB) at 0 and 1500 Hz. The EEG was monitored on an oscilloscope, and acquisition of data was interrupted when voltage exceeded 100 μV or when there was evidence of artificial muscle activity. Data were digitized at a rate of 1000 Hz for on-line averaging, and simultaneous averages were recorded from lateral canthus electro-oculography (EOG) electrodes and monitored in order to exclude EOG contribution to the data. The artifact rejection was automated by computer program and preset to exclude any sweep that was larger than 90% of the A-to-D capacity for amplitude and that exceeded 15% of the entire sweep for duration. With these exclusion parameters it was felt that EOG artifact as well as other artifacts (e.g., swallowing, minor muscular movement) would be fully removed. Grass S-88 stimulator-generated clicks of 0.04-msec duration were amplified within a band width of 20–10,000 Hz and delivered through earphones with a mean intensity of 75 dB, as measured by a sound meter at the earphone.

Stimuli were presented as a series of paired conditioning and testing stimuli. As described by Freedman et al. (8), the interval between the pairs of stimuli was kept

**FIGURE 1. Representative Data for One Normal Subject on P50 Area Responses to Two Click Stimuli Averaged Over 60 Trials[a]**



[a] Robust sensory gating is indicated by the large decrement in the area of the P50 wave following the second click relative to that following the first click.

constant at 10 seconds, and the interval between the conditioning and test pulses was kept constant at 500 msec in order to test the previously identified interval of maximal differences between schizophrenic and normal subjects in this paradigm. Sixty pairs of responses were averaged. The P50 response data were analyzed as follows. Averaged evoked potentials were measured for peak amplitude and area of the P50 wave. The P50 peak was defined as the maximal positive activity occurring between 25 and 75 msec after the stimulus and corresponds to peak amplitude data. Both amplitudes and areas were measured by two methods: 1) from prestimulus baseline to peak and 2) from trough to peak by using the segments of potential immediately preceding and following the P50 peak to construct the local baseline. This second method was used in order to avoid all possible problems caused by a small P50 peak riding on a large, long-lasting negative potential and those associated with using a short interval between conditioning and test stimuli (i.e., 500 msec). Analyses of peak amplitude and area measurements of absolute and relative change scores yielded similar results. Therefore, only area data are reported.

Three specific prospective hypotheses for P50 area responses were formulated. 1) A gating effect would be observed across both groups of subjects and all electrode positions and would be evidenced by a decrement in average P50 response to the second click relative to that of the conditioning first click stimulus. 2) If schizophrenic patients lack robust gating, then the overall decrement in the P50 wave from the response to the first click stimulus to the response to the second click stimulus would be larger in the normal group than in the schizophrenic group (the Diagnosis by Gating interaction). 3) The hypothesized "hypofrontality" in schizophrenic subjects led to the prediction that regional differences between the two groups would be found. Specifically, the magnitude of the differences in P50 responses between normal and schizophrenic subjects would vary among electrode positions, being largest at the frontal electrode position and smallest at the parietal position (the Electrode Position by Diagnosis by Gating interaction).

A three-way repeated measures multivariate analysis of variance (MANOVA) was conducted using BMDP software (17, 18). The MANOVA included a factor for diagnosis (normal or schizophrenic subjects), a repeated measures factor for the stimulus presentations (stimulus 1, the conditioning click; and stimulus 2, the test click), and a factor for the repeated measures at the three electrode positions (frontal, central, and parietal). A square root transformation of P50 area data was used to preserve assumptions of homogeneity of variance and normality.

## RESULTS

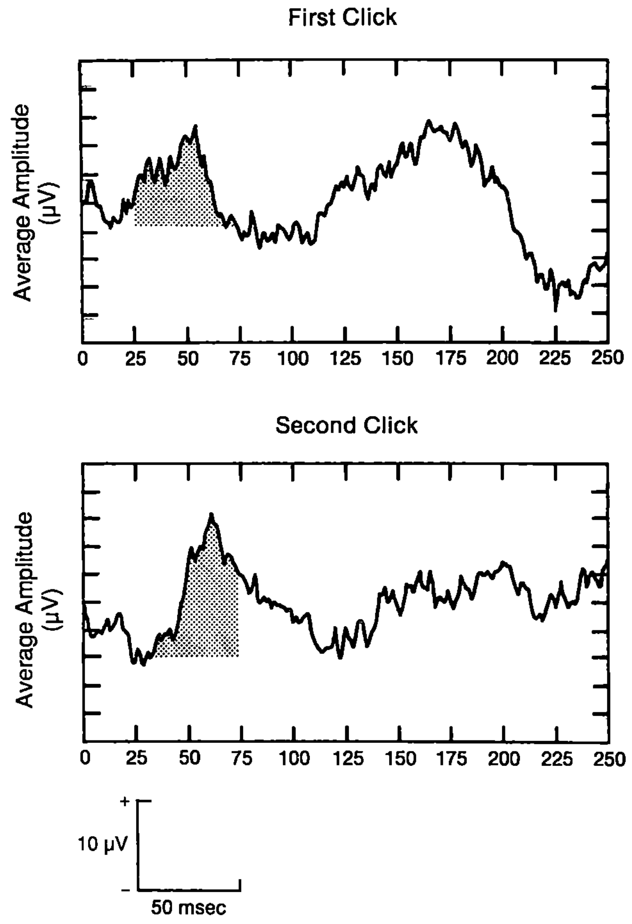
Figures 1 and 2 show averaged P50 area responses to the first and second clicks for one representative subject from the normal group and one from the schizophrenic group, respectively.

### *Primary Analysis*

A significant gating effect was observed in the P50 area response. Across both groups and all three electrode positions, the mean P50 area response to the experimental second click was significantly diminished from that of the conditioning first click (gating effect, $F=176.98$, $df=1, 38$, $p<0.0001$). The mean absolute change scores for the square root of P50 area responses are shown in table 1. The mean relative P50 change score was also significant ($F=281.83$, $df=1, 38$, $p<0.0001$).

A Diagnosis by Gating interaction was evident in the P50 area response. Across all electrode positions the schizophrenic group had a smaller change in the P50 area response from the first to the second click than did the normal group (Diagnosis by Gating interaction, $F=73.33$, $df=1, 38$, $p<0.0001$). It is interesting to note that these significant differences in the decrements can be

**FIGURE 2. Representative Data for One Schizophrenic Subject on P50 Area Responses to Two Click Stimuli Averaged Over 60 Trials[a]**



[a] Loss of normal sensory gating is reflected in the large P50 wave after the second click.

attributed to two separate differences between the two subject groups. That is, the schizophrenic group had a smaller mean P50 area response to the conditioning first click than did the normal group (F=4.34. df=1, 38, p<0.05). The schizophrenic group also had a significantly larger mean P50 area response to the experimental second click than did the normal group (F=21.20, df=1, 38, p<0.0001). Overall, the magnitude of differences between the two groups was fivefold or greater, depending on the electrode placement examined.

There was no significant Electrode Position by Diagnosis by Gating interaction. A multivariate approach to repeated measures was adopted, and since electrode placement was a repeated measures factor with more than two levels (i.e., frontal, central, and parietal), the test for significance for electrode placement effects used in this analysis was Hotelling's $T^2$ test (19). The overall Diagnosis by Gating by Electrode Position interaction was not significant ($T^2$=2.08; F=1.01, df=2, 37, p=0.37). There was a trend in the normal group for the differences between the P50 area responses to the first and second clicks to lessen progressively from the frontal to the parietal electrode positions (i.e., more gating frontally). The opposite trend was noted in the schizophrenic group: the difference between the P50 area responses to the first and second clicks increased progressively from the frontal to the parietal electrode positions (i.e., less gating frontally), as reflected in figure 3.

**TABLE 1. P50 Wave Area Responses of Normal and Schizophrenic Subjects to Two Click Stimuli**

| | P50 Response (μV)[a] | | | |
|---|---|---|---|---|
| | Normal Subjects (N=20) | | Schizophrenic Subjects (N=20) | |
| Stimulus and Electrode Placement | Mean | SE | Mean | SE |
| Conditioning (first click) | | | | |
| Frontal | 13.26 | 0.83 | 10.92 | 0.59 |
| Central | 12.43 | 0.77 | 10.28 | 0.63 |
| Parietal | 11.59 | 0.86 | 10.22 | 0.76 |
| Test (second click) | | | | |
| Frontal | 5.76 | 0.54 | 9.68 | 0.70 |
| Central | 5.17 | 0.53 | 8.68 | 0.70 |
| Parietal | 5.09 | 0.51 | 8.45 | 0.75 |
| Absolute change from conditioning to test | | | | |
| Frontal | –7.50 | 0.70 | –1.24 | 0.57 |
| Central | –7.26 | 0.53 | –1.60 | 0.53 |
| Parietal | –6.50 | 0.62 | –1.77 | 0.53 |

[a] With square root transformation.

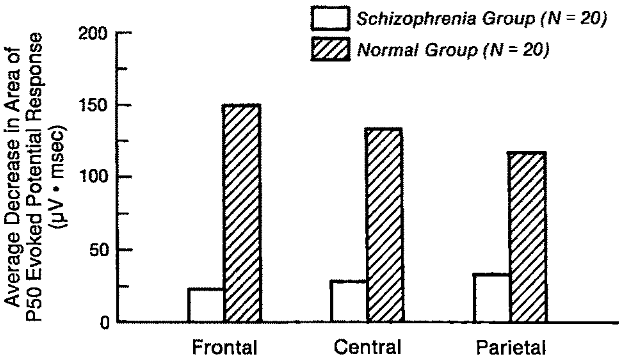
### *Secondary Analyses*

There was a significant difference in mean level of education between the two groups. The mean was 16.20 years (SD=2.75) for the normal subjects and 12.45 years (SD=1.23) for the schizophrenic subjects. However, statistical controls for this difference, using analyses of variance with education levels as covariates, did not change the pattern of results, nor has level of education been reported to affect sensory gating, especially at this observed order of magnitude.

Electrode position affected the magnitude of P50 area response. Across both study groups and both stimulus clicks, the effect of electrode position on the P50 area response was largest at the frontal electrode and smallest at the parietal electrode. This same trend was observed for each combination of subject group and stimulus. The remaining effects—the main effect of diagnosis, the Diagnosis by Electrode Position interaction, and the Gating by Electrode Position interaction—were all nonsignificant.

Sex and age were factors in gating. None of the effects on P50 area tested in the three-way MANOVA changed their significant or nonsignificant status when tested in the five-way MANOVA. However, there were three additional significant effects. The age effect was significant (F=8.59, df=1, 32, p<0.01), with older subjects having larger P50 area responses than younger subjects. The Age by Sex interaction was significant (F=8.57, df= 1, 32, p<0.01). Among younger subjects, males had slightly larger P50 area responses than females (young

**FIGURE 3. Robust Sensory Gating of Normal Subjects and Impaired Gating of Schizophrenic Patients at Frontal, Central, and Parietal Electrode Placement Sites**



males, mean=8.9 μV, SD=1.9; young females, mean= 7.6 μV, SD=1.8); among older subjects, females had larger P50 area responses than males (older females, mean=12.2 μV, SD=1.7; older males, mean=9.1 μV, SD=2.8). The Age by Gating by Electrode Position interaction was significant ($T^2$=13.48; F=6.53, df=2, 31, $p<0.005$). Whereas some details of the difference in P50 area response pattern between younger and older subjects depended on whether the decrement from the first to the second click was measured in absolute square root of P50 area response or in relative change in square root of P50 area response, a consistent finding was that older subjects had their largest mean decrement at the parietal electrode position, and younger subjects had their smallest mean decrement at the parietal electrode position.

## DISCUSSION

The finding that schizophrenic subjects show impaired gating when the P50 conditioning test paradigm is used confirms observations of Freedman and associates (7–9). The normal subjects in this study showed robust sensory gating, whereas the schizophrenic patients showed impaired gating at the frontal, central, and parietal electrode sites. This group difference requires continued scrutiny in larger samples in order to assess the contributions of paradigmatic manipulations, intelligence, education, age, sex, medications, neurotransmitter concentrations, psychological states, and other relevant factors. Also, the relation of sensory gating failures to other information-processing deficits and clinical state and trait variables needs clarification. The functional significance of gating deficits in schizophrenic patients remains speculative. The most common assumption is that the individual is subject to sensory overload when normal gating mechanisms fail, which leads to cognitive fragmentation (1, 20, 21) and may result in the secondary formation of psychotic symptoms (22), although the exact sequencing of these events remains ambiguous and in need of experimental identification.

Potential mechanisms underlying the deficits in sensory gating have been investigated using animal models. Adler et al. (11) invoked the concept of hyperexcitable neuronal systems as a general construct. Swerdlow et al. (23) used the prepulse inhibition or sensorimotor gating of the startle response and found that nucleus accumbens dopamine overactivity induces sensorimotor gating failures parallel to those seen in schizophrenic patients (16). Further, direct infusion of dopamine into the nucleus accumbens (24) and systemic administration of $D_2$ but not $D_1$ agonists (25) produce similar losses of sensorimotor gating. It is possible that such increased subcortical dopamine tone is correlated with the inhibition of frontal brain activity, known as hypofrontality (26, 27), which may be related to gating failures. Supporting this view, the types of stimulus interactions used in our study ("proactive interference") have recently been interpreted as frontal-lobe-based functions (28). In a recent preliminary report, Butler et al. (29) found that paranoid schizophrenic patients with the greatest number of perseverative responses on the Wisconsin Card Sorting Test also showed the greatest loss of tactile but not auditory sensorimotor gating. Since the perseverative response measure of the Wisconsin Card Sorting Test has been reported to be correlated with frontal lobe damage (30), it is possible that both that test and various gating paradigms tap into a common dimension related to hypofrontality, perhaps associated with increased subcortical dopamine activity. Although the evidence in support of hypofrontality is mixed, increased subcortical dopamine activity is consistent with positron emission tomography findings that the mean metabolic centroid is more ventral and caudal in schizophrenic patients than it is in control subjects (31).

Last, it is important to note that the power difference between a 1.5-msec and a 0.04-msec click is so profound (i.e., 37.5 times) that differences between schizophrenic and control subjects could easily have been eliminated in the Kathmann and Engel study (10) by this difference alone. Our own results, with the use of a 0.04-msec click duration, seem to confirm that the increased click power played a role in eliminating the schizophrenia-related P50 gating deficits in that study, perhaps through mechanisms related to suprathreshold stimuli yielding asymptotic data for all groups tested. Future studies may usefully explore multiple click durations among the same subjects in order to clarify fully this issue. In human (20) and animal (32) studies of prepulse inhibition, subtle-appearing paradigmatic manipulations of stimulus intensity and background noise can have profound effects on sensorimotor gating. We have previously pointed out (20) that these information-processing functions often operate at threshold values, where minor experimental paradigmatic changes yield major differences. Thus, it is not surprising that Kathmann and Engel did not reproduce Freedman and associates' finding (7–9) of decreased gating in schizophrenic as compared to normal subjects when the power of the click stimulus was increased manyfold.

In this study, we observed a nonsignificant trend for the schizophrenia-linked gating deficits to be more pronounced in the frontal than in the posterior loci, and this trend needs further examination to see whether a specific subgroup of schizophrenic patients accounts for the gating deficit. Extensions of this research should evaluate the influence of the number of trials used and various interstimulus intervals. Importantly, the relation between reported decreases in regional cerebral blood flow in frontal and temporal lobes in schizophrenic patients (33) and event-related potentials responses in sensory gating paradigms needs to be clarified, as do the contributions of many other factors, including generalized and specific symptoms, neurotransmitter binders, and schizophrenic subtypes. Despite these residual issues, our study strongly confirms the finding of Freedman and associates that compared with normal subjects, schizophrenic patients show a loss of normal sensory gating.

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# Bizarre Delusions and *DSM-III-R* Schizophrenia

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Objective: *Bizarre delusions are assigned greater weight relative to other delusions in the* DSM-III-R *diagnosis of schizophrenia. The decision to emphasize bizarre delusions was based largely on historical tradition rather than empirical evidence. This study examined 1) the extent to which a history of bizarre delusions contributes to the diagnosis of schizophrenia and 2) whether schizophrenic patients with bizarre delusions constitute a clinically distinguishable subgroup.* Method: *Two hundred fourteen consecutively admitted psychotic inpatients were assessed for bizarre delusions according to the* DSM-III-R *criteria. Clinical and demographic correlates of bizarre delusions were examined in subsets of patients diagnosed as schizophrenic according to* DSM-III-R *who also received CT scans and neuropsychological testing.* Results: *With the base prevalence rate for schizophrenia of 0.71, bizarre delusions had a sensitivity of 0.79, a specificity of 0.56, and a positive predictive power of 0.82 for the diagnosis of schizophrenia (N=152) relative to other psychotic disorders (N=62). Clinical, neurobehavioral, CT scan, and premorbid adjustment data on the schizophrenic patients indicated that beyond manifesting more severe positive symptoms, patients with bizarre delusions did not otherwise constitute a clinically distinguishable subgroup.* Conclusions: *The data suggest that criterion A for the diagnosis of schizophrenia in* DSM-IV *could be improved by removing the special emphasis that was placed on bizarre delusions in* DSM-III-R.

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For decades clinicians and researchers have been seeking disease-specific or pathognomonic indicators of schizophrenia. The markedly strange, fantastic, and idiosyncratic content of certain delusions has been thought by some to be a unique hallmark of schizophrenia. Despite the absence of empirical evidence, these so-called bizarre delusions (defined in *DSM-III-R* as delusions "involving a phenomenon that the person's culture would regard as totally implausible") were given greater weight relative to nonbizarre delusions in the *DSM-III-R* criteria for schizophrenia. As part of the effort to validate symptom criteria for inclusion in *DSM-IV,* there is a need for systematic investigation of the value of giving special significance to bizarre delusions in the criteria for the diagnosis of schizophrenia.

According to *DSM-III-R,* the presence of bizarre delusions is by itself sufficient to meet the psychotic symptoms requirement that constitutes criterion A for the diagnosis of schizophrenia. If delusions are not bizarre, the patient must demonstrate at least one additional psychotic symptom to meet this criterion. For some psychotic patients, therefore, the differential diagnosis of delusional disorder versus schizophrenia depends on whether their delusions are judged to be bizarre (1, 2).

From a historical perspective, the concept of bizarre delusions is a vestige of Schneider's (3) first-rank symptoms, which included delusions of being controlled, thought broadcasting, and thought insertion or withdrawal. Although Schneider suggested that these symptoms should be considered pathognomonic of schizophrenia, subsequent studies have not supported this notion (4). Carpenter et al. (5) found that first-rank symptoms do appear frequently in schizophrenia but are by no means exclusive to schizophrenia. Moreover, they found that frequent diagnostic errors are made if these symptoms are viewed as pathognomonic. Other investigators have reported findings consistent with this conclusion (6, 7). Although there is some evidence that first-rank symptoms may have some discriminative value in distinguishing among psychotic disorders (8),

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**TABLE 1. Characteristics of 214 Inpatients With Psychotic Disorders**

| Variable | Schizophrenic Disorders[a] (N=152) N | % | Delusional Depression (N=11) N | % | Bipolar Disorder[b] (N=36) N | % | Delusional Disorder (N=11) N | % | Other Psychotic Disorders[c] (N=4) N | % |
|---|---|---|---|---|---|---|---|---|---|---|
| Bizarre delusions present | 120 | 78.9 | 4 | 36.4 | 19 | 52.8 | 0 | 0.0 | 4 | 100.0 |
| Male sex | 85 | 56.0 | 5 | 45.5 | 13 | 36.1 | 6 | 54.5 | 1 | 25.0 |
| Marital status[d] | | | | | | | | | | |
| Never married | 117 | 77.0 | 8 | 72.7 | 17 | 47.2 | 9 | 81.8 | 2 | 50.0 |
| Married | 12 | 7.9 | 2 | 18.2 | 10 | 27.8 | 1 | 9.1 | 1 | 25.0 |
| Previously married | 23 | 15.1 | 1 | 9.1 | 9 | 25.0 | 1 | 9.1 | 1 | 25.0 |
| Race | | | | | | | | | | |
| White | 97 | 64.0 | 10 | 90.9 | 28 | 77.8 | 8 | 72.7 | 2 | 50.0 |
| Black | 38 | 24.7 | 1 | 9.1 | 5 | 13.9 | 2 | 18.2 | 1 | 25.0 |
| Other | 17 | 11.3 | 0 | 0.0 | 3 | 8.3 | 1 | 9.1 | 1 | 25.0 |
| Socioeconomic status | | | | | | | | | | |
| I | 2 | 1.4 | 1 | 9.1 | 1 | 2.9 | 0 | 0.0 | 0 | 0.0 |
| II | 18 | 11.9 | 3 | 27.3 | 8 | 20.6 | 3 | 27.3 | 0 | 0.0 |
| III | 49 | 32.2 | 2 | 18.2 | 19 | 52.9 | 2 | 18.2 | 2 | 50.0 |
| IV | 40 | 26.6 | 2 | 18.2 | 5 | 14.7 | 4 | 36.4 | 1 | 25.0 |
| V | 43 | 28.0 | 3 | 27.3 | 3 | 8.8 | 2 | 18.2 | 1 | 25.0 |

[a] Includes *DSM-III-R* schizophrenia, schizophreniform disorder, and schizoaffective disorder.
[b] Manic episode.
[c] Includes brief reactive psychosis (N=2) and psychotic disorder not otherwise specified (N=2).
[d] Significant difference between groups ($\chi^2$=17.18, df=8, p<0.05).

there is considerable variability in estimates of the prevalence of these symptoms in schizophrenia, ranging from as high as 72% (9) to as low as 28% (10). It is important to note, however, that most studies have considered first-rank symptoms collectively, leaving the specific value of the bizarre delusion criterion relatively unexplored.

Findings on the prognostic value of first-rank symptoms have also been contradictory. Taylor (10) and Harrow et al. (11, 12) concluded that schizophrenic patients with first-rank symptoms showed poorer outcome than patients without first-rank symptoms, but Strauss and Carpenter (13) and Hawk et al. (14) found no relation between outcome and the presence or absence of these symptoms. Kendell et al. (15) concluded that Schneider's first-rank symptoms were among the poorest predictors of social and symptomatic outcome when compared to five alternative operational definitions of schizophrenia.

In the present study, we investigated the diagnostic efficiency (16–18) of bizarre delusions and the relation between bizarre delusions and other clinical features of hospitalized schizophrenic patients. In particular, we asked, 1) To what extent does the presence of a history of bizarre delusions contribute to the diagnosis of schizophrenia? and 2) Do schizophrenic patients with bizarre delusions differ from other schizophrenic patients on key demographic and/or clinical features?

## METHOD

Subjects were recruited from among psychotic inpatients consecutively admitted to a psychiatric teaching hospital. Thorough screening of new admissions to the hospital was conducted daily. Patients with histories of neurologic or significant medical illness or substance abuse/dependence disorders that might confound diagnosis or clinical presentation were excluded from the study.

The 214 subjects were aged 18–55 years. On the basis of information gathered with the Structured Clinical Interview for DSM-III-R (SCID) (19), the patients had the following diagnoses: schizophrenia (N=119), schizoaffective disorder (N=26), schizophreniform disorder (N=7), bipolar disorder with psychotic features (N=36), major depression with psychotic features (N=11), delusional disorder (N=11), psychotic disorder not otherwise specified (N=2), and brief reactive psychosis (N=2). The mean age was 31.4 years (SD=8.6) for the 152 patients with schizophrenic disorders, 33.1 years (SD=9.6) for the patients with bipolar disorder, 28.4 years (SD=10.4) for the patients with depression with psychotic features, 33.0 years (SD=8.2) for the patients with delusional disorder, and 29.8 years (SD=8.0) for the four patients with other psychotic disorders. Age and other demographic characteristics were essentially equivalent across diagnostic groups, with the exception of marital status (table 1). A higher percentage of the patients with bipolar and other psychotic disorders were currently or had been previously married.

The lifetime histories of bizarre delusions of the 214 patients were determined using *DSM-III-R* criteria. Three raters, independently and without knowledge of final diagnoses, reviewed written transcripts of relevant data collected in the SCID interviews and determined whether or not each reported delusion qualified as bizarre. The kappa coefficient for the three independent raters was 0.78. For the final data analysis, discrepancies between ratings were resolved through discussion

**TABLE 2. Diagnostic Efficiency[a] of Bizarre Delusions in Differentiating Schizophrenic Disorders From Other Psychotic Disorders**

| Bizarre Delusions | Patients With Schizophrenic Disorders (N=152) | Patients With Other Psychotic Disorders (N=62) | Total (N=214) |
|---|---|---|---|
| Present | 120(a) | 27(b) | 147 |
| Absent | 32(c) | 35(d) | 67 |

[a] For the calculations, patients with delusional disorder (N=11) were included in the group with other psychotic disorders. Base prevalence rate of schizophrenic disorders=number of schizophrenic patients/total number of patients: 152/214=0.71. Sensitivity=a/number of schizophrenic patients: 120/152=0.79. Specificity=d/number of patients with other psychotic disorders: 35/62=0.56. Positive predictive power=a/(a+b): 120/147=0.82. Negative predictive power=d/(c+d): 35/67=0.52. Meehl and Rosen's (16) index of diagnostic efficiency: prevalence (P)/(1–P)>(false positive rate)/(true positive rate): 0.71/(1.0–0.71)>(27/62)/(120/152).

until a consensus judgment was obtained; additional opinions of senior clinicians were used when necessary.

From the group of 119 patients diagnosed as having *DSM-III-R* schizophrenia, a subset of 81 patients was included in an intensive clinical assessment study. These patients were predominantly single (74.1%, N=60), and their mean age was 31.8 years (SD=9.0); 61.7% (N=50) were white, 29.6% (N=24) were black, and 8.6% (N=7) were "other." They came from a broad distribution of socioeconomic strata: 12.3% (N=10) from levels I and II (upper and upper-middle class), 30.9% (N=25) from level III (middle class), 27.2% (N=22) from level IV (lower-middle class), and 29.6% (N=24) from level V (lower class). The following clinical dimensions were assessed: 1) the global level of current functioning, with the Global Assessment Scale (GAS) (20); 2) the severity of general symptoms, with the Brief Psychiatric Rating Scale (BPRS) (21); and 3) the severity of specific positive and negative symptoms, with the Scale for the Assessment of Positive Symptoms (22) and the Scale for the Assessment of Negative Symptoms (23). We also used the Cannon-Spoor Premorbid Adjustment Scale (24) to assess levels of social, sexual, academic, and occupational functioning at various developmental stages prior to the onset of illness. The interviews for this scale were conducted with each of the patients near the time of discharge. When available, family members were interviewed to provide additional information on the patients' premorbid adjustment.

Neurobehavioral tests and CT scans were done on patients (N=65) who qualified for study on the basis of the following criteria: no known systemic or neurologic illness by history and by physical examination, no prior ECT, no history of head trauma or substance dependence, and no significant substance abuse within 1 month before testing (and for eye movement measures, no lithium or benzodiazepines within 2 weeks before testing). Neurobehavioral assessments included 1) a battery of neuropsychological tests (Wisconsin Card Sorting Test, Rey Verbal Learning Test, Block Design, Benton Judgment of Line Orientation, F-A-S Verbal Fluency, Finger Tapping, Trail-Making, and Ammons' IQ test), 2) pursuit eye movement testing, and 3) a CT scan for calculating the ventricle-brain ratio (VBR) of the lateral ventricles and frontal horns, by procedures reported elsewhere (25).

## RESULTS

A history of bizarre delusions was documented for 78.9% (N=120) of the 152 patients with "broad-band" schizophrenic disorders (i.e., schizophrenia, schizoaffective disorder, and schizophreniform disorder) (table 1). Prevalence rates were essentially equivalent for the patients with schizophrenia (79.0%, N=94), schizoaffective disorder (80.8%, N=21), and schizophreniform disorder (71.4%, N=5)($\chi^2$=0.29, df=2, n.s.). A history of bizarre delusions was present in 43.5% (N=27) of the patients with nonschizophrenic psychotic disorders, a significantly lower prevalence rate than that for the group with broad-band schizophrenic disorders ($\chi^2$=24.04, df=1, $p<0.0001$).

Seven of the 214 patients met the *DSM-III-R* psychotic symptom criterion for schizophrenia solely on the basis of the presence of bizarre delusions. Thus, 3.3% of all of the psychotic patients and 4.6% of all of the patients with *DSM-III-R* schizophrenic disorders would have failed to qualify for a diagnosis of schizophrenia if bizarre delusions had not been a "sufficient" psychotic symptom in the *DSM-III-R* criterion A for schizophrenia. If bizarre delusions had not been given special emphasis in the diagnosis of schizophrenia, two of these seven patients would have met the *DSM-III-R* criteria for delusional disorder. They did not show a pattern of bizarre behavior, and although chronically psychotic, they had demonstrated intact functioning until shortly before admission. The remaining five patients would have been assigned to the *DSM-III-R* category of psychotic disorder not otherwise specified. Of the seven patients who would no longer be considered schizophrenic, six had experienced their first psychotic episode within the previous 12 months.

Compared to the base prevalence rate for schizophrenia of 0.71 in this sample (table 2), a history of bizarre delusions had a diagnostic sensitivity of 0.79 and a specificity of 0.56. This symptom showed a relatively high positive predictive power of 0.82, indicating that 82% of the patients with histories of bizarre delusions received the *DSM-III-R* diagnosis of schizophrenia. The negative predictive power of 0.52 indicates that 52% of the patients who did not have this symptom received *DSM-III-R* psychotic disorder diagnoses other than schizophrenia.

As one approach to assessing the diagnostic efficiency of the bizarre delusion symptom, we used Meehl and Rosen's base-rate-corrected evaluation of classification accuracy (16). This index (footnote to table 2) indicates whether a certain symptom or test value improves the classification accuracy above and beyond reliance on the base rate alone. In this sample, the index of diagnostic inaccuracy (the false positive rate [0.44] divided by the true positive rate [0.79], i.e., 0.56) was exceeded by

**TABLE 3. Psychiatric Scale Scores at Admission for a Subgroup of 81 Schizophrenic Patients With and Without Bizarre Delusions**

| | Patients With Bizarre Delusions (N=64) | | Patients Without Bizarre Delusions (N=17) | |
|---|---|---|---|---|
| Scale | Mean | SD | Mean | SD |
| Scale for the Assessment of Positive Symptoms[a] | 11.6 | 3.1 | 7.6 | 3.4 |
| Scale for the Assessment of Negative Symptoms | 14.0 | 3.6 | 15.3 | 3.0 |
| BPRS[b] | 55.2 | 9.9 | 48.2 | 8.4 |
| GAS[c] | 25.0 | 5.7 | 29.2 | 5.9 |

[a] Significant difference between groups (t=4.62, df=73, p<0.001).
[b] Significant difference between groups (t=2.65, df=79, p<0.01).
[c] Significant difference between groups (t=2.61, df=79, p<0.01).

**TABLE 4. Prognostic Indicators for a Subgroup of 81 Schizophrenic Patients With and Without Bizarre Delusions**

| | Patients With Bizarre Delusions (N=64) | | Patients Without Bizarre Delusions (N=17) | |
|---|---|---|---|---|
| Prognostic Indicator | Mean | SD | Mean | SD |
| Age at onset (years) | 23.7 | 6.7 | 22.4 | 7.9 |
| Duration of illness (years) | 8.2 | 8.2 | 7.6 | 7.1 |
| Number of previous hospitalizations | 4.0 | 11.1 | 2.7 | 2.8 |
| Premorbid adjustment score[a] | 0.42 | 0.15 | 0.40 | 0.14 |
| Length of index hospitalization (days)[b] | 47.3 | 41.9 | 79.6 | 61.0 |

[a] As measured with the Cannon-Spoor Premorbid Adjustment Scale (24). Scores can range from 0.00 to 1.00; lower scores indicate better adjustment.
[b] Significant difference between groups (t=2.55, df=79, p<0.02).

the index of prevalence (the positive base rate of schizophrenia in the sample [0.71] divided by the negative base rate [0.29], which is equivalent to 2.45). This indicates that the accuracy of diagnosis when the presence or absence of a history of bizarre delusions was used exceeded the base rate of the disorder in our sample (footnote to table 2). A z test of the significance of the difference in proportions indicated that the efficiency of diagnosis based on the symptom criterion (0.82) was statistically greater in magnitude than that attained using the base rate alone (0.71) (z=2.38, p<0.009).

Because according to the *DSM-III-R* criteria, a patient with delusional disorder cannot have bizarre delusions, the preceding analyses may have yielded an artificially high estimate of the diagnostic specificity of bizarre delusions. For this reason, a second analysis was conducted in which patients with *DSM-III-R* delusional disorder were excluded from the group with nonschizophrenic psychoses. In this case, bizarre delusions were found in 52.9% of the patients with nonschizophrenic psychoses—still a significantly lower prevalence than for the broad-band schizophrenia group ($\chi^2$=12.93, df=1, p<0.0003). With the revised, now higher, base rate of 0.75 for schizophrenia, the specificity of bizarre delusions dropped from 0.56 to 0.47, and the negative predictive power dropped from 0.52 to 0.43. Using the revised base rate in the computation of the Meehl and Rosen index, we found that the bizarre delusion criterion still added meaningfully to diagnostic classification beyond the base rate alone in identifying cases of *DSM-III-R* schizophrenia.

To determine whether schizophrenic patients with bizarre delusions represent a clinically distinctive subgroup, we examined the demographic and clinical characteristics of 81 of the 119 patients with *DSM-III-R* schizophrenia for whom extensive clinical assessments were available. This group included 64 patients with and 17 patients without histories of bizarre delusions. Comparisons of the demographic characteristics of these two groups showed no significant differences in age, sex, marital status, race, or socioeconomic status.

We determined the relation between a history of bizarre delusions and admission ratings of symptom severity (with the scales for positive and negative symptoms and the BPRS) and global functioning (with the GAS). The results (table 3) indicated that patients with histories of bizarre delusions showed significantly more severe positive symptoms, as measured by the sum of the global ratings from the Scale for the Assessment of Positive Symptoms. Hallucinations and delusions, as assessed on the global scales from that instrument, were significantly more severe among the patients with bizarre delusions (t=4.48, df=78, p<0.001, and t=2.54, df=79, p<0.02, respectively). Patients with histories of bizarre delusions also had more severe general psychopathology on admission (as measured by total BPRS scores) than those who did not have histories of bizarre delusions. At admission no significant differences between groups were found on the negative symptom dimensions of the Scale for the Assessment of Negative Symptoms. Global functioning at admission, as measured by the GAS, was poorer for the patients with histories of bizarre delusions when compared with the other patients.

Results of neurobehavioral assessment revealed that the patients with histories of bizarre delusions had *fewer* perseverative errors on the Wisconsin Card Sorting Test (t=2.03, df=64, p<0.05), a trend for *smaller* VBR of the frontal horns (t=1.93, df=64, p<0.05) but not the body of the lateral ventricles, and higher IQs (t=3.49, df=64, p<0.01). There were no significant differences on other neuropsychological tests or in gain of pursuit eye movements.

Finally, we investigated the relation between a history of bizarre delusions and clinical factors often considered to be prognostic indicators (age at onset, number of previous hospitalizations, duration of illness, premorbid adjustment, and length of stay during the index hospitalization). The results (table 4) indicated no significant differences between the two groups, with a single exception: patients with histories of bizarre delusions had a significantly shorter hospital stay.

## DISCUSSION

The nosological changes introduced by *DSM-III-R* gave greater weight to bizarre delusions than to nonbizarre delusions in the differential diagnosis of schizophrenia. The assessment of lifetime histories of bizarre delusions among patients with psychotic disorders revealed that bizarre delusions are characteristic of a sizable majority (78.9%) of patients with schizophrenic disorders but are also found with relatively high prevalence (43.5%) in patients with other *DSM-III-R* psychotic disorders. These findings are consistent with previous studies that disputed the pathognomonic character of these symptoms on the basis of prevalence data obtained for various psychotic disorders (5–8).

With use of the Meehl and Rosen index of classification accuracy, the bizarre delusion symptom proved more "efficient" than the schizophrenia base rate alone in accurately classifying cases in our sample into the schizophrenia and nonschizophrenia categories. (On the basis of the ratio of false positives to true positives for our sample, Meehl and Rosen's index of classification accuracy indicates that use of the bizarre delusion symptom would yield more accurate classification than that obtained by using the base rate alone in settings with a base rate for schizophrenia, among psychotic disorders, of 36% or more.) This indicates merely that patients with bizarre delusions were more likely to have schizophrenia than any other psychotic disorder, even with a correction for the base rate of the syndrome.

A more stringent criterion of efficiency is reflected by the number of cases in which the diagnosis of the target disorder would change with a change in the presence or absence of the criterion symptom. In the case of the bizarre delusion symptom criterion, we found that elimination of the extra emphasis on bizarre delusions in criterion A of the *DSM-III-R* definition of schizophrenia would result in only a relatively small number of changes in diagnosis (3%–4%) among a heterogeneous group of patients with psychotic disorders. All but one of the patients diagnosed as having schizophrenia on the basis of meeting this criterion were first-hospitalization patients in the early phase of illness. Although bizarre delusions may offer an advantage for earlier detection of schizophrenia, it is not clear whether all such patients would go on to meet the other diagnostic criteria for schizophrenia. Examination of the patients in our sample who had been ill for 5 years or longer and had histories of bizarre delusions revealed that all of them also had histories of other psychotic symptoms. Therefore, it is possible that over the course of the illness, the diagnosis may become less contingent on the presence of bizarre delusions alone. This suggests that, from a nosological point of view, the bizarre delusion symptom criterion could be dropped as a sufficient psychotic symptom without significantly changing clinical diagnostic practice. The possible cost of delaying the diagnosis of schizophrenia in a small percentage of first-episode patients would be offset by the lack of evidence that this diagnosis is suitable for such individuals.

Comparison of the clinical characteristics of patients with and without histories of bizarre delusions revealed that patients with bizarre delusions had more severe psychotic symptoms at the height of the index episode. Several explanations may account for the more severe positive symptoms in these patients. In patients who presented with bizarre delusions during the target hospitalization, the bizarreness of the delusions might have accounted for the severity of the positive symptom ratings. However, global ratings of hallucinations were also higher for patients with histories of bizarre delusions, suggesting that the elevated global positive symptom ratings were not attributable to bizarre delusions alone. This suggests that schizophrenic patients with histories of bizarre delusions tend to become more acutely psychotic during exacerbations of illness.

Other than the more florid positive symptoms during acute exacerbations, there were no significant differences between schizophrenic patients with and without bizarre delusions in demographic characteristics, premorbid adjustment, or age at onset of illness. Patients with histories of bizarre delusions actually stayed fewer days in the hospital. From the neurocognitive assessment data, there was no indication that a history of bizarre delusions was associated with a more severely disabling illness. In fact, trends in the data were for patients with bizarre delusions to manifest fewer neuropsychological and neuroanatomic impairments. Thus, in terms of factors often thought to be associated with a poorer course of illness (such as premorbid adjustment, age at onset, length of hospital stay, negative symptoms, and neuropsychological and neuroanatomic abnormalities), patients with bizarre delusions were not clinically distinguishable from those without bizarre delusions. In sum, these data do not support the notion that a history of bizarre delusions is prognostic of a more severe form of illness.

Another important issue in evaluating the utility of bizarre delusions as a diagnostic criterion for schizophrenia is the extent to which delusions can be reliably classified as bizarre. Many investigators have noted that it is often difficult to reach agreement among even the most experienced of practitioners (26, and personal communication from K. Kendler, 1990). The *DSM-III-R* definition of "bizarre," based as it is on implausibility rather than physical impossibility, was intended to enhance the clarity of the definition and thus to increase potential interrater agreement on its presence or absence. Nonetheless, there still remains some lack of clarity about what constitutes an implausible delusion. For example, a Hispanic patient who reports spirit possession, or a fundamentalist Christian professing to be controlled by Jesus, or an anxious city dweller who avoids use of the subway because he is convinced that exposure to the electromagnetic field is giving him cancer could present problematic determinations for the clinician. Given the diversity of ethnic and cultural belief systems, and advances in modern technology that tend to blur the distinctions between science fiction and physical fact, it is often difficult to come to a categorical determination of the implausibility of a belief. Nevertheless, the relatively high kappa rate obtained in this study (0.78) demonstrates that a reasonable degree of reliability can be achieved with use of the current operational definition. However, it is likely that our interrater reliability estimate approaches an upper limit, because our assessment team met regularly over a period of years and conducted weekly live interviews and consensus reviews of diagnostic data.

In summary, although bizarre delusions are often presented by patients with schizophrenia, psychotic patients in other *DSM-III-R* categories also show a high prevalence of these delusions. Few patients in our sample met the psychotic symptom criterion for schizophrenia solely on the basis of the presence of a history of bizarre delusions. Patients with bizarre delusions showed more severe positive symptoms at admission; however, on demographic, premorbid adjustment, neurocognitive, and all other clinical measures, there was no evidence that the presence of a history of bizarre delusions reflected a more pathological form of illness. Whereas there may be merit in retaining the bizarre delusion symptom in the exclusion criteria for the diagnosis of delusional disorder, retaining it in the inclusion criteria for schizophrenia appears to add an unnecessary level of complexity to the diagnosis of schizophrenia, with little obvious benefit for clinical practice. Taken as a whole, our data suggest that criterion A for *DSM-IV* could be improved by removing the special emphasis that was placed on bizarre delusions in *DSM-III-R*.

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# Haloperidol Plasma Levels and Clinical Response: A Therapeutic Window Relationship

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*Objective: The purpose of the study was to assess the relationship between plasma haloperidol and clinical response. Method: Sixty-nine newly admitted drug-free schizophrenic men were randomly assigned to receive haloperidol, 5, 10, or 20 mg daily for 4 weeks, and clinical response was measured at the end of the fixed-dose period. Haloperidol was assayed by a sensitive and specific radioimmunoassay. Results: The authors found a curvilinear relationship between clinical response and plasma haloperidol during fixed-dose treatment, with an apparent optimum between 5 and 12 ng/ml. When plasma levels above 12 ng/ml were lowered to the 5–12 ng/ml range, all patients improved to varying degrees and no patient deteriorated. When plasma levels of nonresponders within this therapeutic window were raised above 12 ng/ml (as in routine practice), they, on balance, deteriorated in that they became more dysphoric. With the 20-mg dose, half the patients had plasma levels above 12 ng/ml. Conclusions: In this sample of newly admitted schizophrenic men, optimal clinical response occurred with a plasma haloperidol range of 5–12 ng/ml.*

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To detect a relationship between plasma haloperidol levels and clinical response, patients need to be treated with a fixed dose of haloperidol. Preferably, patients are randomly assigned to a low, moderate, and high dose so that both ends of the therapeutic window (if such exists) are represented. Variable-dose studies tend to produce artifactual therapeutic windows (1).

Four fixed-dose studies with haloperidol suggest a therapeutic window relationship between plasma haloperidol and clinical response. The suggested optimal drug concentrations are 6.5–16 ng/ml (2), 3–11 ng/ml (3), 4–11 ng/ml (4), and 4–22 ng/ml (5). Six fixed-dose studies did not find a therapeutic window relationship, but they were so designed that detection of a therapeutic window relationship (if such exists) was unlikely. Two of the studies (6, 7) used primarily poor neuroleptic responders; three used such low doses—5 versus 10 mg (8), 6 mg (9), and 0.2 mg/kg (10)—that detection of an upper toxic limit was unlikely; and three used doses too high—60 versus 120 mg (7), 0.4 mg/kg (6), and 30 mg (11)—to have plasma levels in the subtherapeutic range. In other words, of the 10 fixed-dose studies with haloperidol, four, in retrospect, were designed properly, and these four found a therapeutic window.

In the four studies (2–5) that suggested a therapeutic range, there were only 26 patients that defined the proposed toxic range, and 17 of these were in Potkin et al.'s investigation (5) of Chinese schizophrenic patients, in which the curvilinear fit explained only 8% of the variance of clinical improvement. Further, these studies failed to discuss the clinical state of patients with high, supraoptimal haloperidol levels. Do such patients appear overmedicated, and, more importantly, do they improve when plasma levels are lowered? This study addresses these issues. The matter is important, for if a therapeutic window relationship exists, it could have significant implications for clinical practice. In particular, the dose would be reduced in some nonresponding patients.

## METHOD

### *Subjects*

The subjects were 82 newly admitted, drug-free (for at least 2 weeks but usually several months) schizophrenic men. They had given informed consent, and

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each patient suffered from a schizophrenic disorder (*DSM-III-R*) without significant physical disease or drug or alcohol addiction. Patients with a history of nonresponse to neuroleptic drugs were excluded, as were those who had a history of severe extrapyramidal side effects with high-potency neuroleptics. Those with a history of poor compliance with medication or treatment also were excluded. Patients were observed in a drug-free state (except for chloral hydrate) for at least 3 days, and none started treatment with haloperidol as long as there was an indication of spontaneous improvement.

Characteristics of the 69 patients who completed the study are detailed in table 1. The patients' ages averaged in the early 30s, and the patients averaged four previous hospitalizations. They had all served in the armed forces, had worked for a mean of 4.5 years at some time, were judged markedly ill on a nurses' rating scale, and had scored at least moderate on conceptual disorganization, unusual thought content, or hallucinatory behavior on the Brief Psychiatric Rating Scale (BPRS) (12). In fact, their mean baseline BPRS Schizophrenia factor score was 13 (normal=3, maximum=21), indicating that they were quite psychotic at baseline. Very excited or menacing patients were not included.

**TABLE 1. Characteristics of 69 Schizophrenic Men**

| Item | Mean | SD | N | % |
|---|---|---|---|---|
| Age (years) | 34.2 | 9.3 | | |
| Previous admissions | 4.3 | 4.5 | | |
| Age at onset of psychotic symptoms (years) | 23.6 | 4.9 | | |
| Race | | | | |
| Black | | | 37 | 53 |
| Caucasian | | | 30 | 44 |
| Hispanic | | | 2 | 3 |
| Living status | | | | |
| Alone | | | 35 | 51 |
| Family | | | 31 | 45 |
| Board and care | | | 3 | 4 |
| Longest continuing period of employment (years) | 4.5 | 3.7 | | |
| Nurses' rating of degree of mental illness at baseline[a] | 4.9 | 1.1 | | |
| Baseline BPRS score | | | | |
| Total[b] | 49.6 | 9.7 | | |
| Schizophrenia factor[c] | 13.1 | 3.2 | | |

[a] 4=Moderately ill, 5=markedly ill, 6=severely ill.
[b] Perfect score=19.
[c] Perfect score=3.

### *Procedure*

The 82 patients were assigned to receive haloperidol, 5, 10, or 20 mg daily for 4 weeks. Patients were assigned by cohort. The first 38 eligible patients were given the 10-mg dose, the next 22 eligible patients were given the 5-mg dose, and the next 22 eligible patients were given the 20-mg daily dose. Assignment to dose was independent of the patient's presenting clinical symptoms. Of the 82 patients, haloperidol plasma levels were available for 69 (of the 13 subjects lost from the study, four eloped, four had protocol violations, three refused blood drawing, and all blood samples were lost for two patients). In case of nonresponse, the physician could increase (or decrease) the dose for another 4 weeks according to clinical judgment. Clinical response was measured at baseline, weekly for the first 4 weeks, and at week 8 after the flexible-dose period. Clinical ratings were made by clinicians who were blind to plasma levels.

Clinical status was assessed weekly in semistructured interviews with the first author (T.V.P.), using the BPRS and the Clinical Global Impression (CGI) (13). The rater was not blind to dose. Extrapyramidal side effects were rated with the Involuntary Movement and Extrapyramidal Side Effects Scale (unpublished manuscript; copies available on request from Dr. Van Putten). On this scale akathisia is scored on a 7-point scale and akinesia is rated for decreases in facial expression, gestures, spontaneous movement, and speed of movement.

Haloperidol was assayed by a sensitive and specific radioimmunoassay (14, 15) capable of detecting 0.5 ng/ml of haloperidol with a within-sample variance (standard deviation/mean) of less than 10%. All samples from each subject were analyzed together in the same batch. The maximum intra-assay and interassay coefficient of variation was 12%, as determined by multiple serum pool replicates analyzed repeatedly in all assays. Blood was drawn weekly in the morning, 10 to 12 hours after the last dose.

### *Data Analysis*

Haloperidol plasma levels were averaged during fixed- dose treatment, and clinical change was measured by the change from baseline on the BPRS Psychosis cluster (Thought Disturbance and Hostile Suspiciousness clusters). Mean haloperidol plasma levels had an estimated reliability (intraclass correlation) of 0.83. These data were fit to a theoretical model that proposed the presence of two sigmoidal plasma level-effect functions, one representing positive treatment response (i.e., increasing BPRS Psychosis improvement scores) and the other representing negative effects (i.e., decreasing BPRS Psychosis improvement scores), as suggested by Teicher and Baldessarini (15). In this two-component model, the predicted BPRS change score is obtained by subtracting the negative component from the positive component.

Each of the two hypothesized components is defined by its slope, minimum and maximum values. The full six-parameter model was initially estimated by using nonlinear regression (16). Very high correlations among the parameters, extremely large coefficients of variation, and poor convergence suggested that a simpler model might be better in this data set. A four-parameter model with equal slopes appeared to be optimal, yielding the same pseudo-$R^2$ (0.46) as the full model. In the final model, coefficients of variation ranged from –0.28 to 0.34, and correlations between parameters ranged from –0.86 to 0.54.

FIGURE 1. Two Sigmoidal Functions of Outcome in Relation to Plasma Haloperidol Concentrations in 69 Schizophrenic Men

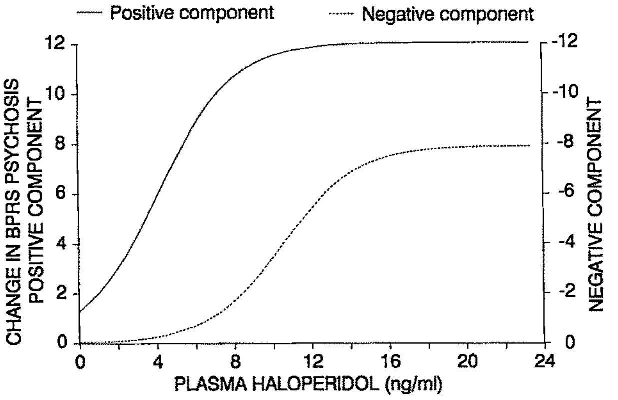

FIGURE 2. Curvilinear Relationship Between Plasma Haloperidol Concentration and Change in BPRS Psychosis Factor for 69 Schizophrenic Men

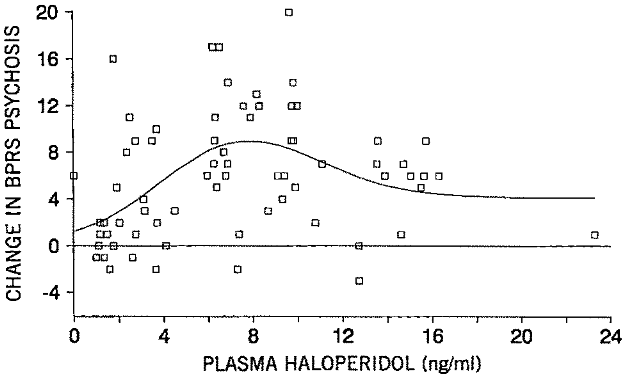

TABLE 2. Scores of 69 Schizophrenic Men on the BPRS Psychosis Factor After Haloperidol Treatment

| Haloperidol Plasma Level Range (ng/ml) | BPRS Psychosis Factor Score |  | N |
|---|---|---|---|
|  | Mean | SD |  |
| Ineffective (<2) | 2.4 | 4.9 | 12 |
| Threshold (2–5) | 4.2 | 4.4 | 14 |
| Optimal (5–12) | 8.8 | 5.0 | 30 |
| Suboptimal (>12) | 4.6 | 3.7 | 13 |

## RESULTS

Figure 1 shows the two sigmoidal dose-effect curves. Negative responses start at about 8 ng/ml and plateau at about 15 ng/ml. Positive treatment response plateaus at about 10 ng/ml. If we subtract the negative from the positive response curve, the resultant curve appears to fit the data rather well (r=0.46, df=66, p=0.001).

Figure 2 shows this two-component model superimposed on the scatterplot of change in the BPRS Psychosis factor versus mean plasma haloperidol. By inspection, it appears reasonable to divide the data into the following nanogram/milliliter ranges: less than 2 (ineffective), 2–5 (threshold), 5–12 (optimal), and more than 12 (suboptimal or toxic). Mean improvement on the BPRS Psychosis factor was significantly greater by t test in the optimal than in the suboptimal range (p=0.004) or the threshold range (p=0.004) (table 2). Mean improvement in the optimal range was roughly twice that in the threshold and suboptimal ranges. The standardized effect sizes were both large (0.95 and 0.90, respectively).

Thirteen patients had mean plasma haloperidol levels above 12 ng/ml at the end of the fixed-dose period. Three insisted on leaving the hospital before a dose adjustment was possible (all had become more paranoid [mean BPRS Paranoia score=–3.5, SD=2.5], and two had become extremely dysphoric). One patient with a mean plasma haloperidol level of 15.6 ng/ml insisted that he required more haloperidol, and his plasma level eventually reached 90 ng/ml (see Discussion). Another patient with a plasma haloperidol level of 14.7 ng/ml was mildly retarded (BPRS Withdrawal-Retardation score=–2) but refused dose reduction. When the plasma haloperidol levels of the remaining eight patients were reduced to less than 12 ng/ml (range=4.0–10.8 ng/ml, mean=7.8), they experienced milder side effects (in particular, a subjective sense of sedation or objective akinesia) and became less psychotic (N=5), less dysphoric (N=3), and less retarded (N=8). No patient deteriorated. Two patients had developed peculiar delusions of bodily destruction, which vanished as the plasma level was lowered. Table 3 summarizes these changes.

In eight relative nonresponders (defined as patients with a global improvement rating of minimally improved or less) with plasma levels in the 2–12 ng/ml range, the plasma level was raised above 12 ng/ml (range=12.9–24 ng/ml, mean=17.8) by increasing mean daily dose from 9.2 mg (SD=2.0) to 23.3 (SD=7.5). Six of eight patients became worse on the global improvement ratings, and, on balance, these six became more dysphoric. Table 4 summarizes the changes.

Figure 2 suggests a threshold limit of 2 ng/ml. If so, patients with plasma levels lower than 2 ng/ml at the end of the fixed-dose period should improve as the plasma level is raised to 2–12 ng/ml. Patients with plasma levels of 1.8, 1.5, 1.6, 1.1, 1.1, and 1.4 ng/ml all improved (with the CGI as the criterion) as their plasma levels rose above 2.0 ng/ml (the plasma levels at which improvement occurred were 2.9, 2.6, 2.1, 2.2, 2.0, and 6.7 ng/ml, respectively). One man with a plasma level of 1.8 ng/ml improved remarkably.

## DISCUSSION

A curvilinear relationship was found between plasma haloperidol and clinical response when patients were given fixed doses of haloperidol. The approximate upper and lower limits of this proposed therapeutic window were 12 and 5 ng/ml, respectively, with 2 ng/ml as a threshold level. When plasma haloperidol levels in relative nonresponders were pushed beyond 12 ng/ml

**TABLE 3. Change in BPRS Scores of Eight Schizophrenic Men When Plasma Haloperidol Levels Were Reduced to Less Than 12 ng/ml**

| | | | Change in BPRS Factor Score From Baseline[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Haloperidol Level (ng/ml) | | Schizophrenia | | Depression | | Paranoia | | Withdrawal-Retardation | |
| Weeks | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 1–4 | 15.0 | 2.1 | 5.1 | 1.6 | 1.0 | 4.3 | 2.4 | 2.9 | –2.3 | 3.4 |
| 5–8 | 7.8 | 2.1 | 6.4[b] | 2.2 | 2.8 | 3.8 | 3.0[c] | 3.5 | –0.1[d] | 3.8 |

[a] Higher change scores mean more improvement; a negative score means deterioration.

[b] $t=2.76$, df=7, $p<0.05$; paired t test, two-tailed, for all comparisons.

[c] $t=1.93$, df=7, $p<0.10$.

[d] $t=5.34$, df=7, $p<0.01$.

**TABLE 4. Change in BPRS Scores of Six Schizophrenic Men With Minimal Response When Plasma Haloperidol Levels Were Raised to More Than 12 ng/ml**

| | | | Change in BPRS Factor Score From Baseline[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Haloperidol Level (ng/ml) | | Schizophrenia | | Depression | | Paranoia | | Withdrawal-Retardation | |
| Weeks | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 1–4 | 7.0 | 4.0 | 1.7 | 2.2 | –1.2 | 2.7 | 1.5 | 2.3 | 0.3 | 1.2 |
| 5–8 | 17.8 | 5.0 | 2.7 | 2.0 | –3.8[b] | 4.1 | –0.3 | 2.6 | –1.0 | 2.2 |

[a] Higher change scores mean more improvement; a negative score means deterioration.

[b] $t=2.33$, df=5, $p=0.07$; paired t test, two-tailed.

**TABLE 5. Relationship of Haloperidol Dose and Plasma Level for 69 Schizophrenic Men[a]**

| | | Plasma Level (ng/ml) | | |
|---|---|---|---|---|
| Dose (mg/day) | N | Mean[b] | SD | Range |
| 5 | 21 | 2.2 | 0.9 | 1.0–4.1 |
| 10 | 31 | 7.7 | 3.2 | 0.0–15.6 |
| 20 | 17 | 12.8 | 4.0 | 7.6–23.3 |

[a] Correlation (r) for haloperidol level versus dose=0.78, df=67, $p<0.0001$.

[b] For each patient weekly plasma levels were averaged.

(as in routine clinical practice), they, on balance, worsened. In particular, they became (relative to their status at more moderate plasma levels) more dysphoric (mean BPRS Depression factor score=–2.6, SD=2.8, $p<0.07$) and more withdrawn (mean BPRS Withdrawal-Retardation factor score=1.3, SD=2.6, n.s.) and did not improve in global psychosis ratings (mean Schizophrenia and Paranoia factor score=–0.83, SD=3.4, n.s.).

Similarly, when patients with plasma levels higher than 12 ng/ml had their plasma levels lowered, they, on balance, improved (change in mean BPRS Schizophrenia factor score of 1.25, $p<0.05$; change in mean Withdrawal-Retardation factor of 2.1, $p<0.01$). No patient deteriorated. Some improved in that they no longer appeared overmedicated in terms of a subjective sedation or objective akinesia. Three patients with plasma levels higher than 12 ng/ml had become globally worse, developed a frantic agitation, and insisted on leaving the hospital before plasma levels could be lowered (two of these patients had become profoundly depressed). Finally, two patients had developed delusions of bodily destruction, which disappeared as the plasma level was lowered.

The division of the data into ineffective, threshold, optimal, and suboptimal ranges was by informal estimation and must be regarded as an approximation. For example, the upper limit of the optimal range could well be drawn at 10 ng/ml. Clinically, the most important is the suboptimal or toxic range (higher than 12 ng/ml), which contained only 13 patients. While plasma level reduction into the 5–12 ng/ml range in eight of these 13 patients resulted in improved psychosis ratings, the same or greater improvement in psychosis ratings (but not in withdrawal-retardation ratings) could have occurred had these patients been exposed to another 4 weeks of the same suboptimal plasma level. To confirm a toxic or suboptimal range, half the patients in the toxic range would need to be randomly assigned to the 5–12 ng/ml range, and the other half would need to remain at the toxic level. Therefore, a clear decrease in antipsychotic effect at a haloperidol level above 12 ng/ml has not been demonstrated.

We also do not mean to imply that patients with plasma levels above 12 ng/ml (table 5) do not improve relative to baseline (after all, many schizophrenic patients in the United States are treated with plasma levels above 12 ng/ml). Table 6 dichotomizes patients into very much or much improved versus minimal improvement, no change, or minimally worse. Five of 13 patients were rated improved at plasma levels higher than 12 ng/ml. In addition, some patients tolerated very high plasma levels. One 33-year-old man in the present sample requested more and more haloperidol, claiming that each dosage increase made him feel somewhat better. Finally, at a dose of 90 mg of haloperidol (plasma level=90 ng/ml), he became slightly sedated and developed moderate akathisia and dyskinesia but remained

**TABLE 6. Global Improvement in 68 Schizophrenic Men at End of Fixed-Dose Period of Haloperidol Treatment**

| Haloperidol Plasma Level Range (ng/ml) | Actual Plasma Level (ng/ml) |  | Improvement on CGI[a,b] |  |  |  |  |
|---|---|---|---|---|---|---|---|
|  |  |  | Improved |  | Not Improved |  |  |
|  | Mean | SD | N | % | N | % | Ratio |
| Ineffective(<2) | 1.3 | 0.5 | 1 | 9 | 10 | 91 | 0.10 |
| Threshold (2–5) | 3.2 | 0.7 | 6 | 43 | 8 | 57 | 0.75 |
| Optimal (5–12) | 8.2 | 1.6 | 22 | 73 | 8 | 27 | 2.75 |
| Suboptimal (>12) | 15.2 | 2.7 | 5 | 39 | 8 | 62 | 0.63 |

[a] Improved=very much or much improved; not improved=minimal improvement, no change, or minimally worse.
[b] $\chi^2$=10.75, df=3, p=0.01.

much improved. When his plasma level was decreased to the therapeutic range, he remained improved and had fewer side effects (including dyskinesia).

Since the correlation between dosage and plasma level was high (r=0.78), a plasma level usually does not provide much extra information. On a dose of 10–15 mg/day, nearly all patients would be in the therapeutic window. There are exceptions. For example, Schultz et al. (17) reported a patient who improved with haloperidol at a dose of 5 mg/day, with a surprisingly high plasma haloperidol level of 22 ng/ml; at 15 mg/day, this patient had a plasma level of 64 ng/ml and developed increased psychotic symptoms. When the plasma level was lowered, the psychotic symptoms improved.

Does knowledge of plasma level improve prediction of outcome over and above dose? When a more conventional method of evaluating a curvilinear relationship is used, a curvilinear (quadratic) function of plasma level fits the data better than a quadratic function of dose (plasma: multiple R=0.40, df=2, 66, p=0.003; dose: multiple R=0.28, df=2, 66, p=0.07), and a stepwise multiple regression analysis indicated that plasma level produces a significant increment in multiple R (F=3.75, df=2, 64, p=0.03). Thus, plasma level is the more powerful predictor of outcome.

At a practical level, it would seem prudent to consider dose reduction in any nonresponding patient with a plasma level higher than 12 ng/ml or when doses greater than 20 mg/day are not successful. Similarly, it may also be prudent to measure plasma haloperidol levels in responding patients who are receiving a high dose. If the plasma haloperidol level is higher than 12 ng/ml, a trial of dose reduction may be indicated. Lastly, plasma haloperidol levels may be most informative with drug interactions. For example, carbamazepine is known to reduce plasma haloperidol levels by 50% or more through microsomal enzyme induction (18–21), and other drug interactions are likely to be discovered.

Limitations of this paper are that all patients were men and dose assignment was not done in a blind manner, raising the possibility that knowledge of dose influenced clinical ratings. The relationship between dose and clinical ratings is complicated (22), however, and we do not believe this happened.

The reason why some patients tend not to do as well at plasma levels higher than 12 ng/ml is unknown. It is unclear whether efficacy is lost at high tissue levels or whether adverse effects diminish therapeutic response. Side effects (such as akathisia, akinesia, or confusion) may mimic or worsen psychiatric illness. In our experience, it is difficult to disentangle akinesia from the negative symptoms of schizophrenia or to distinguish between akathisia and psychotic excitement. For example, one patient with a plasma haloperidol level of 14 ng/ml developed the delusion that he had neurosyphilis and would stand motionless in front of the physician's door. When the plasma level was lowered to 7 ng/ml, these symptoms disappeared. We suspect that the catatonic-like behavior was a manifestation of extrapyramidal symptoms, as described by Quitkin et al. (23)—but we cannot prove it because this particular patient had mild akinesia ratings and was judged as having no akathisia. We believe that the rating of neuroleptic side effects is in a primitive state and that the mechanism whereby some patients deteriorate at higher plasma levels is unknown. Finally, in the present sample there was no relationship between plasma haloperidol levels and akathisia or akinesia, whether examined in ranked or unranked order.

A close relationship between haloperidol brain concentrations and effects on dopamine neurons (stimulation of dopa synthesis, elevation of prolactin secretion, blockade of avoidance responses, and antagonism of amphetamine- and apomorphine-induced behavioral stimulation) has been demonstrated in well-controlled animal experiments. It is interesting that optimal brain concentrations for the aforementioned pharmacological effects correspond to plasma concentrations of 8–12 ng/ml in the rat, while threshold concentrations correspond to 2–3 ng/ml (24).

Our proposed estimate of an optimal range of 5 to 12 ng/ml may not apply to chronic, treatment-refractory patients. Certainly, many such patients are managed at plasma levels of haloperidol much greater than 12 ng/ml (25). The fact that such patients, to varying degrees, can tolerate such high levels does not mean that this is their optimal plasma level. Further, the higher plasma levels in some treatment-refractory patients are really used for chemical restraint or result because of our compulsion to do something. Chemical restraint, useful and necessary as this may be, was not a desired endpoint in the present sample; the patients were reasonably cooperative and calm, thought-disordered schizophrenic men, so that these results may not apply to acutely agitated patients.

Our suggested threshold limit of 2.0 ng/ml is similar to the plasma haloperidol level (mean=4.9 ng/ml, SD=2.9) drawn at neuroleptic threshold by McEvoy et al. (26).

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# Alprazolam as a Neuroleptic Adjunct in the Emergency Treatment of Schizophrenia

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*Objective: While neuroleptics remain the mainstay of drug intervention in the emergency management of psychosis, a variety of agents have received study as alternatives or adjuncts to these drugs in an attempt to improve the safety and efficacy of acute treatment. The purposes of this study were to investigate the efficacy and safety of alprazolam as a neuroleptic adjunct for schizophrenic patients in psychotic relapse and to clarify the effects of combination treatment on specific aspects of the psychotic process. Method: Twenty-eight acutely psychotic patients with schizophrenia who were admitted to an emergency psychiatric service were randomly assigned to treatment with either haloperidol and alprazolam or haloperidol with placebo under double-blind conditions. Drug administration lasted 72 hours. Results: Both groups improved significantly. The combination-treated group required significantly less medication and had 56% fewer dystonic reactions. The addition of alprazolam was most effective for symptoms of excitement and uncooperativeness, particularly in the initial hours of treatment. Conclusions: The combination of alprazolam and haloperidol seems to be the most effective for agitated patients, particularly in the first 48 hours of treatment. It may also result in fewer dystonic reactions.*

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While neuroleptics remain the mainstay of drug intervention in the emergency management of psychosis, a variety of agents have received study as alternatives or adjuncts to these drugs in an attempt to improve the safety and efficacy of acute treatment (1). Benzodiazepines have been the subject of increasing investigation in this regard. To date, a number of reports have focused on the use of benzodiazepines alone or in combination with neuroleptics in the acute treatment of psychotic patients (2–8). In such studies the principal effect of the benzodiazepine as neuroleptic adjunct appeared to be a lowering of the total dose of neuroleptic required, primarily to control agitation as a nonspecific symptom of psychosis. In a recent review article comparing antipsychotics and benzodiazepines as rapid tranquilizing agents, Dubin (9) concluded that benzodiazepines are "very effective" for manic patients in this regard but noted that there is not sufficient evidence to permit a similar conclusion about their use for schizophrenia. According to a recent excellent review on the use of benzodiazepines in psychotic disorders (10), 12 studies have examined the usefulness of benzodiazepines as neuroleptic adjuncts in schizophrenia. Among these studies are reports that when benzodiazepines are used as adjuncts they reduce positive (11, 12) and/or negative (12, 13) symptoms, although these effects may not persist (13). The authors also concluded, however, that there is little evidence of an overall benefit from the use of such combinations, other than in a small number of individuals (10).

Most of these studies were based on weekly ratings and therefore are not applicable to emergency treatment. We are aware of only three prospectively designed acute treatment studies of the efficacy of benzodiazepines (alone or with neuroleptics) in groups of psychotic patients that included schizophrenic patients (4, 5, 8). Cohen and Khan (4) reported significantly greater improvement on two overall outcome measures after 4 days in patients receiving more than 2 mg of lorazepam equivalents in combination with a neuroleptic than in patients receiving less than this amount. This study is the only one of the three which used a study group composed exclusively of schizophrenic patients. Garza-Treviño et al. (5) found several combinations of neuroleptics and sedatives to be very effective in controlling agitation in a group of psychotic patients with a variety of diagnoses. Individual psychotic symptoms were not rated. Finally, Arana et al. (8), studying 14 psychotic

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patients (only five of whom were schizophrenic) who were given either lorazepam or lorazepam with haloperidol, found that both treatment groups demonstrated improvements (at 48 hours) on individual ratings of multiple psychotic symptoms, including suspiciousness, hallucinations, unusual thoughts, and conceptual disorganization.

The present study compared the effects of haloperidol alone with those of haloperidol and alprazolam in a group of schizophrenic patients in psychotic relapse, by means of intensive, prospective ratings of psychotic symptoms in the first 72 hours of treatment. Its purpose was twofold: 1) to investigate the efficacy and safety of alprazolam as a neuroleptic adjunct in this clinical population and 2) to clarify the effects of combination treatment on specific psychotic symptoms.

## METHOD

The subjects were recruited from the psychiatric emergency service of a large inner-city hospital. All of the patients in this study were capable of informed consent and entered voluntarily. Each fulfilled the *DSM-III-R* diagnostic criteria for schizophrenia and were actively psychotic at the time of the interview (as evidenced by a minimum score of 12 on an abbreviated version of the Brief Psychiatric Rating Scale, as will be described). All subjects were between the ages of 18 and 60 years and weighed between 100 and 225 lb. Any individual with a coexisting major axis I disorder, significant medical illness, pregnancy, or use of a nonprescription psychoactive drug (including alcohol) within 72 hours before arrival at the hospital was excluded. Urine drug screens for all patients were collected at the initiation of the study, and patients with positive results were also excluded from the analyses. Thirty subjects were originally selected for the study, but two had to be dropped because of positive urine drug screens.

The patients were assessed at baseline with the Scale for the Assessment of Positive Symptoms (SAPS) (14), Scale for the Assessment of Negative Symptoms (SANS) (15), Brief Psychiatric Rating Scale (BPRS) (16), and a subscale consisting of six items in the psychoticism cluster of the BPRS. The six symptoms included in this measure were suspiciousness, conceptual disorganization, hallucinatory behavior, uncooperativeness, unusual thought content, and excitement. The psychoticism subscale was administered every 2 hours for the first 8 hours on day 1 and at 24, 48, and 72 hours by one of the investigators (J.G.B.). The full-scale version of the BPRS was administered by a second investigator (D.M.M.) at baseline and at 24, 48, and 72 hours. This investigator also administered the SAPS and SANS at baseline and a modified version of these two scales at 72 hours. This modified version contained only the items that are based on signs or symptoms assessed during the course of the interview (rather than on prior history) and are therefore sensitive to acute change.

The investigators who administered the scales were blind to each other's ratings, and the latter investigator was blind to the dose and schedule of treatment established on the first day of the protocol. Both investigators were blind to drug assignment. Interrater reliability was found to be very high during a pilot study; interrater reliability estimates varied from 0.76 on the psychoticism subscale of the BPRS to 0.89 on the SANS, as assessed with the intraclass correlation coefficient (17).

The 28 patients were randomly assigned to two treatment conditions under double-blind conditions. One group received 5 mg of haloperidol in oral concentrate form with a 1-mg tablet of alprazolam. The control group received 5 mg of haloperidol with an identically appearing placebo tablet. After each rating interval on day 1, any individual with a score of 12 or higher on the psychoticism subscale of the BPRS was administered a repeat dose of medication. A dose was not administered if the patient's score was less than 12 or if the patient was excessively sedated. The cutoff score of 12 was empirically derived on the basis of pilot work and represents a level of psychopathology at which a patient is relatively stable and additional antipsychotic medication is not indicated. The total dose received on this basis within the first 24 hours was then administered on a b.i.d. basis (if the total dose was even) or t.i.d. basis (if the total dose was odd) on the second and third days. Both groups received their final doses at 8:00 p.m. Each patient received a minimum of two doses within the first 24 hours. After completion of the study, all patients resumed routine neuroleptic treatment (usually haloperidol) without alprazolam.

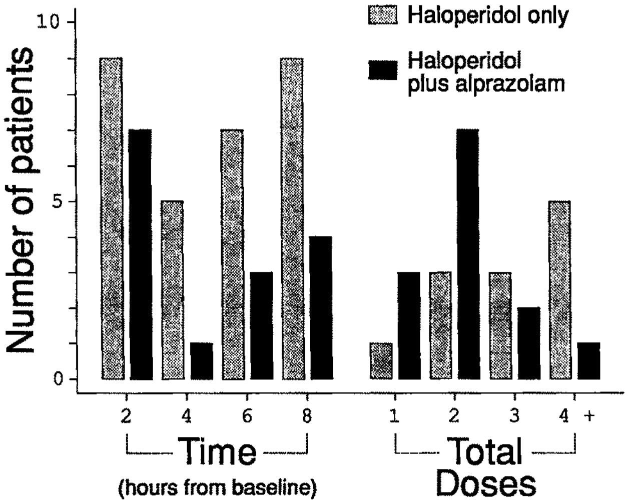
The two groups of 14 subjects each were similar in terms of mean age (haloperidol-only: mean=32.5 years, SD=6.2; combination: mean=33.4 years, SD=5.8), mean weight (haloperidol-only: mean=158 lb, SD=26; combination: mean=158 lb, SD=39), black race (86% and 79%, respectively), and overall level of psychopathology. The proportion of females was higher in the haloperidol-only group (79% versus 43%).

The presence of side effects was assessed with the Simpson-Angus Side Effects Profile (18) and another side effects rating scale (19), which were administered at the completion of the study. The occurrence of dystonic reactions and the frequency with which biperiden was administered to treat these reactions were recorded throughout the study period. A 5-ml sample of blood was drawn between 7:00 and 9:00 a.m. at the conclusion of the study, before institution of routine neuroleptic treatment, in order to measure plasma trough levels of alprazolam and haloperidol. Plasma levels of alprazolam and haloperidol were determined with the gas chromatography techniques described by Greenblatt et al. (20) and Burstein et al. (21).

For humanitarian reasons, patients who had improved sufficiently were discharged from the hospital before the conclusion of the study. In such a case, a final set of ratings (as already described) for the 72-hour assessment were administered before discharge, and these results were included in the analyses.

The test scores were analyzed by using both univari-

**FIGURE 1. Temporal Distribution of Doses and Number of Doses During First Day of Acute Treatment for Schizophrenic Patients Given Haloperidol Only or Haloperidol Plus Alprazolam**[a]



[a] For the haloperidol-only group (N=14), a dose consisted of 5 mg of haloperidol and a placebo tablet; for the combination group (N=14), a dose was 5 mg of haloperidol plus 1 mg of alprazolam. The average total dose was significantly lower in the combination group than in the haloperidol-only group (2.1 versus 3.2 doses; t=2.49, df=19.2, p=0.02).

ate and multivariate techniques, following the guidelines suggested by Looney and Stanley (22). Since the two approaches yielded the same results, only the more familiar univariate results will be reported here. The Greenhouse-Geisser correction was applied in the calculation of p values. Spearman correlations were used to determine the association between the outcome measures and plasma haloperidol level. Spearman correlations were used because these do not assume that the relationship between dose and effect is linear.

## RESULTS

Figure 1 depicts the allocation of doses over the first 8 hours of the study. On day 1, the number of patients in both groups who required medication decreased over hours 0–4 but then increased toward the end of the period. The group that received haloperidol plus alprazolam received significantly fewer doses of medication on day 1.

Scores for each of the measures at each time point are given in table 1. For both groups as a whole the tranquilizing effect (i.e., decrease in score) was found to be significant for the SAPS, the SANS, the BPRS, and the BPRS psychoticism subscale. There were no significant differences between the two groups on any of these measures, at any of the time points, suggesting that the two treatments had similar overall effects. Similar results were found for four of the six items of the psychoticism subscale: suspiciousness, hallucinatory behavior, unusual thought content, and excitement. There were no changes for the group as a whole over the course of the study and no difference between the two groups at any time point on the conceptual disorganization and uncooperativeness subscales.

Nine subjects improved sufficiently to be discharged before the completion of the study (four from the haloperidol-only group and five from the combination group). Those subjects had lower mean baseline scores than the other subjects on the SAPS (t=2.71, df=25, p=0.01) and BPRS psychoticism subscale (t=2.54, df=20.8, p=0.02) but had comparable mean baseline SANS scores. It appears unlikely that their early departure from the study affected the results, as the groups were equally depleted. In addition, the exit ratings, which were completed for all these subjects, were incorporated in the analyses.

The average numbers of side effects were similar in the two groups (an average of about eight). The five most frequent complaints were drowsiness, blurred vision, tremors or shaking, difficulty in concentration, and restlessness. The mean scores on the Simpson-Angus extrapyramidal side effects questionnaire were equivalent.

A total of 16 dystonic reactions occurred in the haloperidol-only group, while only seven occurred in the combination group. The proportion of individuals receiving as-needed medication for dystonic reactions was higher in the haloperidol-only group (64%) than in the combination group (36%). However, there is no statistical evidence to indicate that these differences were significant. This may be because of the small number of subjects.

The plasma alprazolam levels ranged from 0 to 30.1 mg/ml (mean=12.53, SD=7.20). The mean plasma haloperidol level was lower in the haloperidol-only group (mean=2.02 mg/ml, SD=1.5) than in the combination group (mean=3.69 mg/ml, SD=2.6), but the difference was not statistically significant (Wilcoxon test, normal approximation, p=0.12). The mean plasma haloperidol level of the subjects receiving medication on a b.i.d. basis (mean=3.33 mg/ml, SD=2.7) was slightly higher than that of the subjects who received it on a t.i.d. basis (mean=2.27 mg/ml, SD=1.7), but the difference was not statistically significant.

The correlation between the number of doses received and plasma haloperidol level was higher in the combination group (Spearman r=0.63) than in the haloperidol-only group (Spearman r=0.38). Lastly, we were unable to find a significant association between plasma haloperidol level and measures of outcome.

## DISCUSSION

These results demonstrate that both treatment groups improved significantly during the study period and that the patients receiving the combination of haloperidol and alprazolam required significantly less haloperidol to achieve a similar result. The finding that less medication is required in combination therapy for schizophrenic patients supports similar conclusions by previous investigators (7, 8) in retrospective studies of

**TABLE 1. Ratings of Schizophrenic Patients' Psychotic Symptoms Over 72 Hours of Acute Treatment With Haloperidol Only (N=14) or Haloperidol Plus Alprazolam (N=14)**

| | SAPS[a] | | SANS[b] | | BPRS[c] | | BPRS Psychoticism Subscale[d] | |
|---|---|---|---|---|---|---|---|---|
| Time and Group | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 0 hours | | | | | | | | |
| Haloperidol | 60.43 | 15.00 | 46.29 | 23.13 | 34.57 | 8.13 | 18.14 | 3.48 |
| Combination | 48.92 | 23.03 | 44.00 | 14.54 | 31.46 | 7.37 | 18.46 | 6.79 |
| 2 hours | | | | | | | | |
| Haloperidol | — | — | — | — | — | — | 17.00 | 3.23 |
| Combination | — | — | — | — | — | — | 15.07 | 6.50 |
| 4 hours | | | | | | | | |
| Haloperidol | — | — | — | — | — | — | 15.64 | 3.06 |
| Combination | — | — | — | — | — | — | 14.50 | 5.37 |
| 6 hours | | | | | | | | |
| Haloperidol | — | — | — | — | — | — | 16.57 | 3.74 |
| Combination | — | — | — | — | — | — | 14.07 | 6.21 |
| 8 hours | | | | | | | | |
| Haloperidol | — | — | — | — | — | — | 16.00 | 4.21 |
| Combination | — | — | — | — | — | — | 13.93 | 5.18 |
| 24 hours | | | | | | | | |
| Haloperidol | — | — | — | — | 24.85 | 7.14 | 14.08 | 3.50 |
| Combination | — | — | — | — | 24.86 | 11.91 | 14.50 | 5.92 |
| 48 hours | | | | | | | | |
| Haloperidol | — | — | — | — | 19.25 | 5.03 | 11.45 | 4.25 |
| Combination | — | — | — | — | 21.25 | 10.00 | 12.33 | 5.85 |
| 72 hours | | | | | | | | |
| Haloperidol | 26.92 | 15.21 | 20.92 | 11.47 | 20.30 | 6.43 | 11.50 | 5.30 |
| Combination | 27.46 | 21.96 | 23.31 | 11.66 | 27.11 | 10.59 | 14.56 | 4.69 |

[a] Significant decrease in scores for both groups (F=62.20, df=1, 22, p).

[b] Significant decrease in scores for both groups (F=52.52, df=1, 22, p).

[c] Significant decrease in scores for both groups (F=31.15, df=3, 48, p).

[d] Significant decrease for both groups in overall scores (F=15.10, df=7, 119, p) and in scores on the items for suspiciousness (F=8.07, df=7, 105, p=0.0001), hallucinatory behavior (F=10.30, df=7, 105, p=0.0001), unusual thought content (F=4.04, df=7, 105, p=0.01), and excitement (F=3.80, df=7, 105, p=0.007) but not for conceptual disorganization (F=2.01, df=7, 105, p=0.12) or uncooperativeness (F=2.31, df=7, 105, p=0.08).

groups of psychotic patients from multiple diagnostic categories. The data in table 1 also indicate that the patients who received the combination treatment tended to improve throughout the first 8 hours of the study, unlike the patients who received haloperidol alone, who had a more fluctuating course. There was no evidence of paradoxical excitation (a side effect that has been reported with benzodiazepines) or of an association between discontinuation of alprazolam at the end of the study and any adverse effects.

This study does not suggest that the addition of alprazolam to haloperidol results in a significantly greater reduction in the core psychotic symptoms of schizophrenia, e.g., suspiciousness, hallucinations, unusual thoughts, and conceptual disorganization. However, the first dose of the combination treatment did result in greater decrements initially in the ratings of excitement (1.25 points versus 0.43 in the haloperidol-only group) and uncooperativeness (0.80 points versus 0.14), although these did not reach statistical significance. Interestingly, the total BPRS score was actually (nonsignificantly) higher in the combination-treated group at 72 hours, perhaps because the combination-treated group received substantially less haloperidol over time. These results suggest that the primary utility of combination treatment in an emergency setting is in the first 48 hours of treatment, predominantly for the control of agitation and increased arousal.

Although the differences in the occurrence of dystonic reactions and the amount of adjunctive medication to treat these reactions did not reach statistical significance, the subjects in the combination-treated group experienced 56% fewer reactions. Such a reduction may represent a significant clinical advantage for combination therapy. It has been estimated that 90% of dystonic reactions occur within the first 5 days of initiation of neuroleptic treatment (23), and such reactions are a common complication of emergency neuroleptic treatment.

Inferences about the effectiveness of alprazolam as an adjunct to haloperidol within our study design are limited by three factors. First, the two groups did not receive equal amounts of haloperidol, which is a proven antipsychotic agent. The observation that plasma levels of haloperidol tended to be higher in the group that also received alprazolam was surprising, since this group received fewer doses of medication. It is possible that alprazolam may interfere with the metabolism of haloperidol, although to our knowledge there have been no such reports with neuroleptics (24). Results with tricyclic antidepressants, however, have been conflicting (25, 26). If there were such interference, the lower number of doses of medication required by the combination group could be due to the pharmacokinetic effects of alprazolam, rather than to its psychotropic effect.

Second, the doses in the two treatment groups were allocated on an as-needed basis and were the lowest amount possible to calm the patients. Prior reviews on the efficacy of the benzodiazepines in schizophrenia (27, 28) have suggested that one of the major reasons for an apparent lack of efficacy in many studies has been inadequate doses. The plasma values of alprazolam we obtained were at the lower end of the range of the values that have been reported to be therapeutic in nonpsychotic anxiety disorders (29). Douyon et al. (12), in their study of alprazolam as a neuroleptic adjunct for outpatient schizophrenic patients treated for 3 weeks, found that individuals with blood levels higher than 23 ng/ml were more likely to show a significant response.

Third, the relatively small number of subjects in the study, as well as the wide variability of the outcome measures, raises the possibility that significant differences between the two treatment groups were missed. In particular, the alprazolam-treated group had a lower mean SAPS score at baseline, although the difference was not statistically significant. Inspection of the other baseline measures reveals only minimal differences between the two groups in psychopathology ratings, thus suggesting that such differences were not a major factor in the outcome. However, because of the large variability in all of the measures, the presence of differences in the baseline status of the two groups cannot be completely ruled out. The number of subjects available for this study was too small for more elaborate statistical methods, which may have helped in the resolution of this issue.

In conclusion, the combination of alprazolam and haloperidol seems to be the most effective for agitated patients. The severity of the psychopathology of the patients included in our study was limited by our decision to obtain informed consent. Had we included more severely disturbed patients in the study, we believe that differences in the outcomes of the two groups would have been more apparent, particularly on measures of arousal and aggression. From our clinical observations, the patients who are the most severely agitated are the most likely to benefit from combination treatment, especially in the initial hours of emergency treatment.

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# Prospective Study of Neuroleptic-Induced Dystonia in Mania and Schizophrenia

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*Objective: The authors' goal was to conduct a prospective study comparing the rate of occurrence of neuroleptic-induced dystonia in a group of consecutively admitted manic and schizophrenic patients receiving typical inpatient treatment from several clinicians. Method: All patients met the following criteria: 1) male sex, 2) age between 17 and 45 years, 3) definite diagnosis of mania or schizophrenia according to Research Diagnostic Criteria, 4) no exposure to neuroleptics during the past month, 5) absence of past or family history of a neurodegenerative disorder with extrapyramidal symptoms. All treatment decisions were left to the treating clinicians. Fifty patients with mania and 33 with schizophrenia were included in the study. Most of these patients received high-potency neuroleptics, but the specific neuroleptic used varied in the two groups. Results: Twelve (24%) of the patients with mania and five (15%) of the patients with schizophrenia developed acute dystonia. Manic patients received significantly higher peak doses of neuroleptics during the risk period for dystonia. Stepwise multiple regression analysis revealed that the peak neuroleptic dose and age were most strongly related to the occurrence of dystonia. Conclusions: This prospective study failed to support the retrospective finding of another study that acute dystonia occurred more often in manic patients than in patients with nonparanoid schizophrenia. The authors conclude that there is a need for carefully controlled prospective studies with larger groups of patients.*

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Acute dystonic reactions are the most dramatic forms of acute dyskinesias. Some 90% of acute dystonic reactions occur within the first 5 days of neuroleptic treatment (1–3). The reported rates of neuroleptic-induced acute dystonic reactions vary from 2.3% (1) to 63% (4). Risk factors that have been identified include male sex, age younger than 30, higher dose of neuroleptics, and use of high-potency agents (1–9). An analysis of pooled data from nine studies found that the incidence of neuroleptic-induced dystonia without prophylactic anticholinergics was 14.8% in studies using any neuroleptic and 51.2% in studies using only high-potency neuroleptics (10). Drawing from the repeated observations that tardive dyskinesia occurs more often in affective disorders (11–14), Nasrallah et al. (15) hypothesized that acute dystonia may also be more common in affective disorder. In a retrospective study (15) they found a significantly higher incidence of acute dystonia in mania (26.1%) than in nonparanoid schizophrenia (5.9%). Nasrallah et al. included only nonparanoid patients with schizophrenia to eliminate any error due to the possible diagnostic overlap between paranoid schizophrenia and mania with paranoid features. However, Hamra et al. (14) noted a high risk for tardive dyskinesia in both paranoid schizophrenia and affective disorder and, citing Jeste et al. (16), hypothesized that the common denominator could be the "increased noradrenergic activity reported in both conditions, as reflected by low levels of monoamine oxidase and high serum levels of dopamine-β-hyroxylase."

The findings of Nasrallah et al. (15) are interesting. Acknowledging the limitations of their retrospective study, they emphasized the need for prospective studies. We conducted such a study to compare the rate of occurrence of neuroleptic-induced dystonia in a group of consecutively admitted manic and schizophrenic patients receiving typical inpatient treatment from several clinicians.

## METHOD

We included in this study all patients consecutively admitted to our facility who met the following criteria: 1) male sex, 2) age between 17 and 45 years, 3) definite diagnosis of mania or schizophrenia according to Research Diagnostic Criteria, 4) no exposure to neuroleptics

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during the past month, 5) absence of past or family history of a neurodegenerative disorder with extrapyramidal symptoms. All treatment decisions were left to the treating clinicians. The general hospital policy is not to use anticholinergics prophylactically. Patients who received anticholinergics during the first week of neuroleptic treatment were excluded from study. This led to the exclusion of 14 patients for whom anticholinergics were prescribed for moderate to severe pseudoparkinsonism, typically on day 4 or 5 of hospitalization. Equal proportions of patients with mania and patients with schizophrenia were excluded on account of this criterion.

Fifty patients with mania and 33 with schizophrenia were finally included in the study. The mean age of the manic patients was 26.34 years (SD=8.34) and that of the schizophrenic patients was 27.39 (SD=6.59). The difference in age between the two groups was not significant (t=1.01, df=81, n.s.). Twenty-one (42%) of the manic patients were experiencing their first episode of mania; the rest were having their second to sixth episode. The duration of illness among patients with schizophrenia varied from 6 months to 5 years; only four schizophrenic patients had clearly episodic courses. Twelve (36%) of the schizophrenic patients had paranoid type and 21 (64%) had nonparanoid type.

Residents and nurses who were blind to the hypothesis of the study were asked to record explicitly all forms of acute dystonia in all newly admitted patients along with the treatment given and the response to treatment. The diagnosis of dystonia was made by the attending resident on the basis of the sudden onset of twisting or sustained movements, acute discomfort of the patient, and rapid resolution of symptoms after parenteral administration of benztropine mesylate.

High-potency neuroleptics were prescribed for most of the patients, but the specific neuroleptic used varied in the two groups. Forty-six of the patients with mania received haloperidol, three received chlorpromazine, and one received pimozide; only five received lithium in addition to neuroleptics. Among the patients with schizophrenia, seven received haloperidol, 13 received trifluoperazine, four received fluphenazine decanoate, three received chlorpromazine, one received thioridazine, and five received a combination of fluphenazine decanoate and trifluoperazine. For the conversion to chlorpromazine equivalents we used the following formula: 100 mg of chlorpromazine=100 mg of thioridazine=5 mg of trifluoperazine=2.5 mg of haloperidol=2 mg of pimozide. One intramuscular injection of 25 mg of fluphenazine decanoate was considered the equivalent of 291.7 mg/day of chlorpromazine. The conversion formula used was based on tables of suggested dose equivalence (17).

## RESULTS

Seventeen (20%) of the 83 patients developed neuroleptic-induced dystonia. More of the patients with mania (12 of 50) than of the patients with schizophrenia (five of 33) developed dystonia, but the difference between the groups was not statistically significant ($\chi^2$=0.96, df=1). In the schizophrenic group there was no significant difference in dystonic reactions between paranoid (two of 12) and nonparanoid (three of 21) patients ($\chi^2$=0.09, df= 1).

In both groups, acute dystonia occurred more often among those who were younger than 30 years (10 of the 12 patients with mania and four of the five patients with schizophrenia who developed dystonia were younger than 30). Dystonia occurred more often in those receiving haloperidol (13 of 53 manic or schizophrenic patients), trifluoperazine (three of 13 schizophrenic patients) and a combination of fluphenazine decanoate and trifluoperazine (one of five schizophrenic patients). None of the seven patients receiving low-potency neuroleptics (chlorpromazine and thioridazine) had dystonia. When the data for only the patients treated with high-potency neuroleptics were analyzed, 12 (26%) of the 47 patients with mania and five (17%) of the 29 patients with schizophrenia had dystonia, which further diminishes the difference ($\chi^2$=0.70, df=1, n.s.). Only one of the five manic patients receiving lithium in addition to neuroleptics developed dystonia.

Fifty-nine percent (N=10) of the 17 patients who developed dystonia, compared with 26% (N=17) of the 66 patients who did not develop dystonia, received a dose of neuroleptics that was higher than 1 g/day. The difference between these groups was significant ($\chi^2$=6.73, df=1, p=0.01). The mean dose of neuroleptics (in chlorpromazine equivalents) for the first week of treatment was 966.23 mg/day (SD=475.43) for the manic group; for the schizophrenic group it was 588.00 mg/day (SD=459.78). The difference between the two groups was highly significant (t=5.65, df=81, p=0.001). Within the manic group those who had dystonia received significantly higher peak doses (1188.00 mg/day [SD=371.43]) of neuroleptics than those who had no dystonia (896.10 mg/day [SD= 482.29]) (t=2.72, df=48, p=0.01). The peak doses of schizophrenic patients who did or did not develop dystonia did not differ significantly (t=0.49, df=31, n.s.).

Because there was no significant difference between patients with mania and patients with schizophrenia, the data for these groups were pooled for a stepwise multiple regression analysis to determine the variables related to dystonia. The independent variables used as predictors of dystonia included diagnosis, age, mean neuroleptic dose, and peak neuroleptic dose. The strongest correlate was peak neuroleptic dose (F=4.53, df=1, 81, p=0.05). The only other significant correlate was age plus peak neuroleptic dose (F=3.29, df=2, 80, p=0.05). The peak neuroleptic dose explained 5.3% of the total variance, and the addition of age to peak neuroleptic dose increased the percentage of variance explained to 7.6%.

## DISCUSSION

Our prospective study failed to support the retrospective findings of Nasrallah et al. (15). Neuroleptic-induced dystonia occurred with almost equal frequency among patients with mania in our study and theirs. More of our schizophrenic patients developed dystonic reactions (15% compared with 5.9%). Both investigations involved only male subjects exposed to a variety of neuroleptics. However, unlike the study of Nasrallah et al., we included paranoid patients with schizophrenia in our sample and did not find the occurrence of dystonia to differ between paranoid and nonparanoid subtypes. In keeping with the literature, dystonia in our sample occurred more often among patients younger than 30 and those receiving high doses of high-potency neuroleptics. Stepwise multiple regression analysis of the pooled data found that only peak neuroleptic dose made a significant independent contribution to the development of dystonia. The addition of age to peak neuroleptic dose was the only other significant contributor. Thus, the majority of the variance in risk for dystonia was still unaccounted for.

The study by Nasrallah et al. (15) found no significant difference between the mean neuroleptic dose prescribed for the manic and the schizophrenic groups. In our study, manic patients received significantly higher doses of neuroleptics than did patients with schizophrenia. Simpson and Singh (18) suggested that the peak or maximum dose of neuroleptics used may be more informative than the total mean dose. Patients with mania more often receive higher initial doses of neuroleptics that are later reduced as therapeutic levels of lithium are reached and/or the acute symptoms subside. For patients with schizophrenia, however, it is usual to start with relatively smaller doses of neuroleptics that are raised depending on the response. Thus, the total mean dose may conceal the real difference in the dose of neuroleptics used during the risk period for dystonia. It is also possible that there were more young patients with schizophrenia in our study group (mean age=27.39 years) than among the subjects of Nasrallah et al. (age was not reported).

There are two important limitations of this study: the small number of subjects and the substantial difference in the type of neuroleptic used in the two patient groups. However, under typical inpatient treatment conditions, diagnosis was not found to be an important risk factor for neuroleptic-induced dystonia. Peak neuroleptic dose emerged as the single most significant risk factor for dystonia. The estimation of the peak neuroleptic dose was based on a table of suggested dose equivalence, however, and such data are crude at best (19). Thus, there is a need for carefully controlled prospective studies with larger groups of patients.

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# Fatigue, Sleep Disturbance, Disability, and Indices of Progression of HIV Infection

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*Objective: The authors' objective was to test the hypothesis that fatigue affects the activities and employment of subjects with HIV infection and that indices of immunosuppression and inflammation may have statistical utility in predicting fatigue and sleep disturbance. Method: The authors prospectively asked 112 homosexual men (62 HIV-seropositive subjects and 50 HIV-seronegative comparison subjects) to complete a questionnaire on fatigue and sleep disturbance. In addition, hematocrit, WBC count, CD4+ cell number, lactate dehydrogenase, albumin, and total globulin were measured. Results: For HIV-seropositive patients fatigue was significantly more of a problem and interfered more with important activities such as employment and driving than with seronegative comparison subjects. The HIV-infected patients were significantly more likely to be unemployed, to feel fatigued through more hours of the day, to sleep more, to nap more, and to have diminished midmorning alertness. The medical variables could be used to statistically predict fatigue, its interference with daily activities, and employment. Conclusions: Fatigue and sleep disturbances contribute to morbidity and disability in HIV-infected homosexual men, especially those in CDC stage IV (AIDS-related complex or AIDS). Correlation with measures of immunosuppression and inflammation and comparison between fatigued versus nonfatigued groups suggest the possibility of statistical prediction of fatigue by using these measures. Further study is needed to examine the possibility of eventual specific intervention to clinically treat HIV-related fatigue, sleepiness, and sleep disturbance.*

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Fatigue has been associated with the syndrome of HIV infection in all early clinical descriptions (1). In an early case report, tiredness was the chief complaint (2). In acute HIV infection, fatigue is prominent, with lethargy and malaise being reported in 66.7% of homosexual men who became HIV positive (3, 4).

In chronic HIV infection, unexplained fatigue is a prominent persistent symptom (5). Fatigue as measured by the score on the 5-item scale in the Profile of Mood States (POMS) was reported to be significantly higher in a group of 13 patients with AIDS-related complex (ARC) than in 17 HIV-positive subjects with minimal symptoms, 11 seronegative homosexual men, and 22 heterosexual men (6). Fifteen patients with AIDS also had more fatigue than did control subjects, but the difference did not reach statistical significance.

Fatigue may be a uniquely important symptom in HIV infection. In addition to the anguished complaints of HIV patients about this draining fatigue, the impact on public funding may be large. Fatigue can be the overriding symptom that causes individuals to discontinue employment. When they are unable to continue to work, they must turn to public support for subsistence. With loss of employment also comes loss of health insurance coverage in almost all cases. The individuals must then also rely on public funds for health care of this illness, with its prolonged, slowly progressive deterioration.

To test the hypothesis that fatigue affects the activities and employment of HIV-seropositive subjects, fatigue, sleepiness, and disturbances of sleep were prospectively measured and their influence on the morbidity and disability caused by HIV infection was examined. Within this general hypothesis, we further tested whether differences in life disruption existed between

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the CDC stage III and stage IV patients and the comparison subjects. In addition, we examined multiple laboratory indices of disease activity as correlates of fatigue and as statistical predictors of fatigue, sleep disturbance, and employment status. The symptoms that we evaluated, fatigue and sleepiness, are complex and difficult to define. Subjective complaints of fatigue and sleepiness may be a more sensitive measure of CNS impairment than objective, behavioral sleep activities. No standard, objective psychometric instruments exist for the assessment of fatigue and sleepiness, especially their assessment in the context of chronic HIV infection, as will be discussed later. We developed a questionnaire to specifically address problems of subjective fatigue in HIV-positive patients.

## METHOD

Subjects were recruited for this study from a cohort of men in a longitudinal study of over 200 homosexual men. All subjects in the cohort had given informed consent after the nature of the study had been fully explained. A total of 112 homosexual men arriving for consecutive appointments for a scheduled study visit were asked to participate. Of the 112 men, 50 were HIV-negative comparison subjects and 62 were HIV-positive patients. Each of the subjects completed the questionnaire that we developed to evaluate fatigue, sleepiness, and sleep habits in HIV-positive subjects. (The questionnaire is available from Dr. Darko.) In addition, blood samples were drawn to measure hematocrit, WBC count, number of CD4+ cells, lactate dehydrogenase, albumin, and total globulin (defined as total protein minus albumin).

For the purposes of analysis, 108 of the subjects were first divided into three groups on the basis of diagnosis. Group 1 (N=14) consisted of subjects with ARC or AIDS (CDC stage IV) (7). Group 2 (N=44) consisted of HIV-seropositive subjects without symptoms or signs except lymphadenopathy (CDC stage III). Group 3 (N=50) contained the comparison homosexual men who were seronegative for HIV antibodies. (The remaining four HIV-seropositive subjects were without symptoms or lymphadenopathy.) All statistical analyses were performed with standard statistical programs (8, 9). Initially an among-groups comparison (three groups) was performed. Following this comparison, three between-groups comparisons were performed with analysis of variance (ANOVA) (CDC stage IV group versus comparison group, CDC stage III group versus comparison group, and CDC stage IV versus stage III group). Statistical comparisons of the categorical data were made by using the nonparametric chi-square statistic (likelihood ratio), with Yates's correction when appropriate. For brevity of data presentation, multiple-choice items were interpreted dichotomously on the basis of whether the response was positive or negative. There is occasional missing data in the fatigue questionnaire because not all subjects answered all questions. In table 1 the missing data are reflected in subject numbers that are smaller than the total number of subjects in the group. Comparisons of continuous data were made with ANOVA.

To examine the question of which medical indices may be associated with or underlie fatigue and sleep difficulties, Pearson's correlation coefficients were calculated between the continuous fatigue/sleep variables and the six medical indices (hematocrit, WBC, CD4+ cells, lactate dehydrogenase, albumin, and total globulin). The continuous fatigue/sleep variables were question 6 (hours of fatigue felt daily) and question 8 (hours slept at night). In addition, questions 2 (does fatigue interfere with daily activities) and 3 (employment status) (categorical variables) were used as grouping parameters to define new subject groups, and the between-groups differences were examined for the six medical indices by using ANOVA. Further, a discriminant analysis involving canonical discriminant functions used the six medical variables to predict group membership as defined by questions 1 (is fatigue a problem), 2, and 3.

Finally, to examine whether fatigue, sleep, and peripheral blood measures are related independently to the stage of HIV infection, we performed multiple regression on the CDC stage III and IV groups individually. Specifically, laboratory variables were used to statistically predict responses on the fatigue/sleep questions, using discriminant analysis on the CDC stage III and IV groups separately. This technique allowed us to control for factors such as concurrent opportunistic infection, tumor, fever, and zidovudine therapy, which may increase as HIV infection progresses through CDC stages.

## RESULTS

The three groups, patients with ARC or AIDS (CDC stage IV), patients with only lymphadenopathy (CDC stage III), and the HIV-negative comparison subjects, were not statistically different in age (CDC stage IV: mean=36 years, SD=4; CDC stage III: mean=38, SD=6; comparison subjects: mean=38, SD= 10; F=0.31, df=2, 109, p=0.62).

CDC stage IV patients clearly differed from uninfected comparison subjects on fatigue and sleep disturbance, with significant among- and between-group differences on most of the areas examined. Over half of the CDC stage IV patients had problematic fatigue, compared to only 10% of the comparison subjects (table 1, question 1). Half of the CDC stage IV subjects, but none of the comparison subjects, said that fatigue interfered with their daily activities (question 2). Most of the CDC stage IV subjects were not working, compared with less than one in 10 of the comparison subjects (question 3). One in five unemployed CDC stage IV subjects, but none of the unemployed comparison subjects, said that fatigue was largely responsible for the need to stop working (question 5). The CDC stage IV subjects were fatigued through more hours of the day than comparison subjects (question 6). CDC stage

**TABLE 1. Fatigue and Sleep Disturbance Among Homosexual Men With CDC HIV Stages III and IV and Among Comparison Subjects**

| | Stage IV Group (N=14) | | | | Stage III Group (N=44) | | | | Comparison Group (N=50) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Questionnaire Item | N | % | Mean | SD | N | % | Mean | SD | N | % | Mean | SD |
| 1. Is fatigue a problem for you? | | | | | | | | | | | | |
| Never or sometimes | 6 | 43 | | | 39 | 89 | | | 45 | 90 | | |
| Often or always | 8 | 57 | | | 5 | 11 | | | 5 | 10 | | |
| 2. Does the fatigue interfere with your daily activities? | | | | | | | | | | | | |
| Never or sometimes | 7 | 50 | | | 40 | 91 | | | 50 | 100 | | |
| Often or always | 7 | 50 | | | 4 | 9 | | | 0 | 0 | | |
| 3. Are you employed? | | | | | | | | | | | | |
| No | 11 | 85 | | | 5 | 17 | | | 2 | 8 | | |
| Yes | 2 | 15 | | | 25 | 83 | | | 24 | 92 | | |
| 4. If you are employed, does fatigue interfere with your work? | | | | | | | | | | | | |
| Never or sometimes | 12 | 86 | | | 43 | 98 | | | 50 | 100 | | |
| Often or always | 2 | 14 | | | 1 | 2 | | | 0 | 0 | | |
| 5. If you are not employed, but you were, was fatigue part of the reason you stopped working? | | | | | | | | | | | | |
| No or partly | 11 | 79 | | | 44 | 100 | | | 50 | 100 | | |
| Almost or only reason | 3 | 21 | | | 0 | 0 | | | 0 | 0 | | |
| 6. Through how many hours of the day on average do you feel fatigue? | | | 8 | 9 | | | 3 | 4 | | | 1 | 3 |
| 7. Do you fall asleep at times when you do not want to? | | | | | | | | | | | | |
| Never to weekly | 11 | 79 | | | 37 | 84 | | | 47 | 94 | | |
| Two to more than seven times weekly | 3 | 21 | | | 7 | 16 | | | 3 | 6 | | |
| 8. Hours slept at night | | | 9 | 2 | | | 9 | 1 | | | 8 | 1 |
| 9. Do you ever have trouble falling asleep? | | | | | | | | | | | | |
| Never or sometimes | 11 | 79 | | | 37 | 84 | | | 46 | 92 | | |
| Often or always | 3 | 21 | | | 7 | 16 | | | 4 | 8 | | |
| 10. Do you take sleeping pills to help you fall asleep? | | | | | | | | | | | | |
| Never or sometimes | 11 | 79 | | | 38 | 86 | | | 47 | 94 | | |
| Often or always | 3 | 21 | | | 6 | 14 | | | 3 | 6 | | |
| 11. How many times during your usual sleep period do you awaken by yourself and then go back to sleep? | | | | | | | | | | | | |
| Rarely to two | 9 | 64 | | | 36 | 82 | | | 43 | 86 | | |
| Three or more | 5 | 36 | | | 8 | 18 | | | 7 | 14 | | |
| 12. How often does sleepiness interfere with your driving? | | | | | | | | | | | | |
| Less than monthly | 12 | 86 | | | 35 | 79 | | | 49 | 98 | | |
| Monthly or more | 2 | 14 | | | 9 | 21 | | | 1 | 2 | | |
| 13. Do you ever wake up too early and find you cannot go back to sleep? | | | | | | | | | | | | |
| Two days or less weekly | 5 | 62 | | | 29 | 85 | | | 35 | 97 | | |
| Three days or more weekly | 3 | 38 | | | 5 | 15 | | | 1 | 3 | | |
| 14. How often do you take naps? | | | | | | | | | | | | |
| Twice weekly or less | 7 | 50 | | | 35 | 79 | | | 44 | 88 | | |
| Three or more times weekly | 7 | 50 | | | 9 | 21 | | | 6 | 12 | | |
| 15. How long do you usually sleep during your naps? | | | | | | | | | | | | |
| Less than 1 hour | 7 | 50 | | | 22 | 50 | | | 26 | 52 | | |
| More than 1 hour | 7 | 50 | | | 22 | 50 | | | 24 | 48 | | |
| 16. Which choice below best describes how you usually feel for the first 2 or 3 hours after you wake up from your normal sleep period? | | | | | | | | | | | | |
| Alert to relaxed | 4 | 29 | | | 35 | 79 | | | 42 | 84 | | |
| Foggy or worse | 10 | 71 | | | 9 | 21 | | | 8 | 16 | | |
| 17. How many cups of coffee and tea or cans of cola do you drink per day? | | | | | | | | | | | | |
| Less than three | 13 | 93 | | | 33 | 75 | | | 40 | 80 | | |
| Three or more | 1 | 7 | | | 11 | 25 | | | 10 | 20 | | |

[a] For chi-square comparisons among three groups, df=2; for chi-square comparisons between two groups, df=1. For all comparisons, significance was defined as p≤0.05.

[b] Cannot be calculated; the result reflects no difference.

IV subjects slept longer each night than comparison subjects (question 8). Over one-third of the CDC stage IV subjects had frequent early morning awakening, compared to almost none of the comparison subjects (question 13). Fully half of the CDC stage IV patients napped frequently, compared to only 12% of the comparison

**TABLE 1 (continued)**

| Comparisons[a] | | | |
|---|---|---|---|
| Among All Three Groups | Stage IV Versus Comparison | Stage III Versus Comparison | Stage IV Versus Stage III |
| $\chi^2=19.00$<br>p=0.0001 | $\chi^2=12.97$<br>p=0.0003 | $\chi^2=0.05$<br>p=0.80 | $\chi^2=11.44$<br>p=0.0007 |
| $\chi^2=29.99$<br>p<0.00009 | $\chi^2=24.78$<br>p<0.000009 | $\chi^2=6.27$<br>p=0.01 | $\chi^2=10.13$<br>p=0.0001 |
| $\chi^2=29.04$<br>p<0.00009 | $\chi^2=24.38$<br>p<0.000009 | $\chi^2=1.06$<br>p=0.30 | $\chi^2=18.57$<br>p=0.00002 |
| $\chi^2=8.33$<br>p=0.01 | $\chi^2=6.32$<br>p=0.01 | $\chi^2=1.53$<br>p=0.20 | $\chi^2=2.48$<br>p=0.10 |
| $\chi^2=20.72$<br>p<0.00009<br>F=13.54<br>df=2, 105<br>p<0.00009 | $\chi^2=9.67$<br>p=0.002<br>F=2.89<br>df=13.7<br>p=0.01 | —[b]<br><br>F=1.90<br>df=76.0<br>p=0.06 | $\chi^2=9.06$<br>p=0.003<br>F=2.30<br>df=14.7<br>p=0.04 |
| $\chi^2=3.51$<br>p=0.17<br>F=5.37<br>df=2, 98<br>p=0.006 | $\chi^2=2.73$<br>p=0.10<br>F=2.67<br>df=13.9<br>p=0.02 | $\chi^2=2.63$<br>p=0.10<br>F=1.93<br>df=81.1<br>p=0.06 | $\chi^2=0.20$<br>p=0.60<br>F=1.57<br>df=15.7<br>p=0.10 |
| $\chi^2=2.32$<br>p=0.30 | $\chi^2=1.76$<br>p=0.20 | $\chi^2=1.42$<br>p=0.20 | $\chi^2=0.20$<br>p=0.60 |
| $\chi^2=3.11$<br>p=0.20 | $\chi^2=2.48$<br>p=0.10 | $\chi^2=1.59$<br>p=0.20 | $\chi^2=0.50$<br>p=0.50 |
| $\chi^2=3.42$<br>p=0.20 | $\chi^2=3.02$<br>p=0.08 | $\chi^2=0.30$<br>p=0.60 | $\chi^2=1.74$<br>p=0.20 |
| $\chi^2=8.23$<br>p=0.02 | $\chi^2=2.93$<br>p=0.09 | $\chi^2=9.32$<br>p=0.002 | $\chi^2=0.30$<br>p=0.60 |
| $\chi^2=8.32$<br>p=0.02 | $\chi^2=7.08$<br>p=0.008 | $\chi^2=3.42$<br>p=0.06 | $\chi^2=1.90$<br>p=0.20 |
| $\chi^2=9.74$<br>p=0.008 | $\chi^2=8.50$<br>p=0.003 | $\chi^2=1.25$<br>p=0.30 | $\chi^2=4.30$<br>p=0.04 |
| $\chi^2=0.04$<br>p=0.90 | $\chi^2=0.01$<br>p=0.90 | $\chi^2=0.04$<br>p=0.80 | $\chi^2<0.000009$<br>p=1.00 |
| $\chi^2=18.74$<br>p=0.0001 | $\chi^2=15.33$<br>p=0.00009 | $\chi^2=0.31$<br>p=0.60 | $\chi^2=12.03$<br>p=0.00005 |
| $\chi^2=2.09$<br>p=0.30 | $\chi^2=1.49$<br>p=0.20 | $\chi^2=0.34$<br>p=0.60 | $\chi^2=2.45$<br>p=0.10 |

subjects (question 14). Only one-third of CDC stage IV patients felt alert during the morning hours, compared to most of the comparison subjects (question 16).

A statistically significant difference between CDC stage III patients and comparison subjects existed for two questions: fatigue interfering with daily activities and sleepiness while driving (question 12). One of 10 patients said that fatigue interfered with daily activities and one of five experienced sleepiness while driving, compared with none or almost none, respectively, of the comparison subjects (table 1).

The relationship of fatigue to markers of immunosuppression, inflammation, and anemia were pursued by correlational analyses. Patients with lower numbers of CD4+ cells (i.e., those more ill with HIV infection) experienced more hours of daily fatigue (r=–0.19, p=0.05) and required more hours of sleep during the night (r=–0.34, p<0.0009). Higher lactate dehydrogenase levels correlated with more hours of fatigue felt daily (r=0.25, p=0.009) and with more hours slept during the night (r=0.26, p=0.009). Lower hematocrit levels correlated with more hours slept during the night (r=–0.29, p<0.002).

The 112 subjects were next divided on the basis of their response to question 2. The group in whom fatigue did interfere with daily activities had significantly lower numbers of CD4+ cells, significantly higher total globulin, and significantly lower hematocrit than the group in whom fatigue did not interfere with daily activities (table 2).

To assess the relationship between laboratory variables and employment, subjects were divided on the basis of their response to question 3 (employed versus unemployed). The unemployed group had significantly lower hematocrit, significantly lower numbers of CD4+ cells, significantly higher lactate dehydrogenase, significantly lower albumin, and significantly higher total globulin (table 3).

Next, three discriminant analyses were performed by using the medical variables to predict group membership, as defined by the response to fatigue questionnaire questions 1, 2, and 3. For question 1, number of CD4+ cells contributed the most to this grouping, followed in rank order by WBC, total globulin, hematocrit, and lactate dehydrogenase. The membership in the "fatigue not a problem" group was correctly predicted for 75.0% of the patients and membership in the "fatigue a problem" group was correctly predicted for 52.6% of the patients; overall, 71.2% of the patients were correctly classified.

For question 2, group membership was predicted better than for question 1, with CD4+ number being the strongest predictor, followed by WBC, total globulin, hematocrit, and lactate dehydrogenase. Membership in the "fatigue not interfering with daily activities" group was correctly predicted for 74.0% of the patients, and membership in the "fatigue interfering with daily activities" group for 81.8% of the patients; overall, group membership of 74.8% of the patients was correctly classified.

The best prediction of group membership existed for question 3 (employment). Total globulin was the strongest predictor, followed by hematocrit, WBC, CD4+, and lactate dehydrogenase. Membership in the employed group was predicted correctly for 84.9% of

**TABLE 2. Relationship Between HIV-Related Laboratory Measures and Fatigue Among Homosexual Men**

| | Fatigue Interfered With Daily Activities (N=11) | | Fatigue Did Not Interfere (N=97) | | | |
|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | F (df=1, 109) | p |
| Hematocrit (%) | 40 | 5 | 43 | 4 | 3.8 | 0.05 |
| CD4+ T lymphocytes (cells/mm$^3$ blood) | 330 | 222 | 681 | 377 | 8.3 | 0.005 |
| Total globulin (g/100 ml)[a] | 3.4 | 0.6 | 2.9 | 0.6 | 5.8 | 0.02 |

[a] Total protein minus albumin.

**TABLE 3. Relationship Between HIV-Related Laboratory Measures and Employment Status for Homosexual Men**

| | Unemployed (N=18) | | Employed (N=51) | | | |
|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | F (df=1, 69) | p |
| Hematocrit (%) | 39 | 6 | 43 | 3 | 13.4 | <0.0009 |
| CD4+ T lymphocytes (cells/mm$^3$ blood) | 344 | 440 | 690 | 393 | 9.8 | 0.003 |
| Serum lactic dehyrogenase (U/ml) | 221 | 87 | 176 | 54 | 5.1[a] | 0.03 |
| Serum albumin (g/100ml) | 3.9 | 0.7 | 4.2 | 0.2 | 10.4 | 0.002 |
| Total globulin (g/100 ml)[b] | 3.5 | 0.6 | 2.9 | 0.6 | 15.4 | <0.0009 |

[a] df=1, 62.
[b] Total protein minus albumin.

the patients, and membership in the unemployed group for 77.8% of the patients; overall, 83.1% of the patients were correctly classified.

Finally, a further question needed to be resolved. Were these predictions possible simply because the fatigue, sleep, and laboratory measures all worsen independently with worsening stages of HIV infection? To answer this question, we performed multiple regression on the CDC stage III and IV groups individually in order to determine whether the blood measures would predict responses on the fatigue/sleep questions within each CDC stage and discriminant analysis on the CDC stage III and IV groups individually to predict membership in sets as defined by the response to fatigue questionnaire items 1, 2, 3, 12, and 14 within each CDC stage.

When multiple regression of the CDC stage III group was used alone, hematocrit (p=0.008) did significantly predict the number of hours slept at night. On discriminant analyses, the five medical variables did predict group membership as defined by questions 1, 2, and 3, with 72% to 96% correct classification of patients.

When multiple regression on the CDC stage IV group was used alone, WBC (p=0.03) and CD4+ (p=0.01) did significantly predict the number of hours slept at night. On discriminant analyses of the CDC stage IV group alone, the five medical variables did predict group membership as defined by questions 1, 2, 12, and 14, with 83% to 100% correct classification of patients.

## DISCUSSION

This prospective study confirms the previously undocumented clinical impression that fatigue and sleep disturbance are frequent symptoms of advanced HIV infection, contributing to morbidity and disability. When subjects with ARC or AIDS (CDC stage IV) were contrasted with comparison subjects, the difficulties caused by fatigue were dramatically demonstrated. The differences among the three groups were due primarily to the differences between the CDC stage IV (AIDS/ARC) group and the comparison group. Fatigue did interfere with daily activities, and sleepiness interfered with driving, significantly more in the CDC stage III patients than in comparison subjects. It is possible that CDC stage IV patients are no longer driving as much and thus do not notice that fatigue interferes with driving because they do not place themselves at risk. Given the imposed physical immobility and the monotony of the effort, driving may be a relatively sensitive indicator of sleepiness. As expected, the patients with more advanced HIV infection, as evidenced by lower hematocrit and CD4+ cell number and higher lactate dehydrogenase, were troubled by fatigue throughout the day and slept more.

We have tried, using several statistical methodologies, to convince ourselves and the reader that the draining fatigue of which HIV patients complain is a real problem related to the infection. We realize that such statistical associations do not imply causality, and we have planned continuing studies, as described later, to investigate this question and its mechanism. It may be possible to construct statistical models to predict disability based on early changes in medical indices. In a multivariate model, five of the medical variables (CD4+, WBC, total globulin, hematocrit, and lactate dehydrogenase) predicted reasonably well whether or not subjects were troubled by fatigue, whether or not fatigue interfered with their daily activities, and employment status. The role of total globulin in predicting employment status is especially interesting in light of the association of hypergammaglobulinemia and polyclonal B cell activation (10).

The results of analyses in the CDC stage III and IV groups alone demonstrate that the medical variables are not merely independently associated with advancing HIV infection. Instead, within CDC groups, the medical variables remain predictive of the presence of fatigue and its interference with daily activities.

The need for developing a fatigue and sleep questionnaire is worthy of discussion. The POMS does allow the calculation of a fatigue subscore, but it is based on only five items and represents a limited range of aspects of fatigue. The Stanford Sleepiness Scale, meant to be used in conjunction with the polysomnographic Multiple Sleep Latency Test (11, 12), measures only tendency toward sleepiness at the time the scale is administered. The Pittsburgh Sleep Quality Index (13) is intended as a screening instrument for insomnia and does not address fatigue or hypersomnia, such as are found in HIV infection. No instrument existed to survey the fatigue of HIV infection, its effect on daily activities such as work and driving, and possible sleep disturbances that may underlie the fatigue. A revision of this questionnaire is now being used at our HIV Neurobehavioral Research Center (funded by the National Institute of Mental Health [NIMH]) and will allow data collection for standardization, sensitivity, validity, and reliability.

Each of the peripheral blood tests chosen is medically nonspecific in itself and is suggestive of conditions associated with fatigue or sleepiness. For example, elevations of lactate dehydrogenase have been clearly associated with pneumocystis carinii pneumonia, hepatitis, or hemolytic anemias. However, for these indices to have clinical utility in predicting fatigue, it is not necessary that this be independent of predictive utility for medical illness with which fatigue is known to be associated.

A direction for future studies is the examination of specific humoral mediators of fatigue and sleep disturbance in HIV-positive individuals. A convergence of data suggests that HIV-related excess of interferon, tumor necrosis factor, or interleukin-1 may be a cause of the fatigue of HIV infection. Elevated acid-labile interferon-α was one of the first abnormalities described in AIDS (14) and may be a marker for AIDS (15). Interferon-α-2 has been demonstrated to be somnogenic in an animal model (16). Tumor necrosis factor is elevated in sera of CDC stage IV subjects (17–19), and cells from HIV-positive subjects produce increased amounts of tumor necrosis factor (20–23). Elevated levels of interleukin-1 (24) and interleukin-1 inhibitor (25) have been described in the plasma of AIDS patients. Interleukin-1 has been demonstrated in brain tissue and may be produced by astroglial cells (25, 26).

Interferon, tumor necrosis factor, and interleukin-1 are each somnogenic and affect sleep physiology by enhancing slow-wave sleep (26, 27). Interleukin-1 is thought to mediate the induction of slow-wave sleep and fever in animals by muramyl dipeptide (28, 29), a constituent of the slow-wave sleep-enhancing, sleep-promoting factor, Factor S (30). Interleukin-1 has been shown to promote slow-wave sleep and fever in two animal models (31, 32), with the sleep effect persisting when the febrile response was blocked by an antipyretic agent (31). There is evidence that these three cytokines elicit their somnogenic actions through a common regulatory mechanism involving serotonin and glial cells (27). In healthy male control subjects, increased plasma interleukin-1 occurs during sleep, particularly after sleep deprivation (33). This raises the question of whether sleep disturbance could be cause rather than effect.

Disturbed sleep physiology in HIV-infected patients has been reported (34). The seropositive subjects had a higher percentage of slow-wave sleep in the second half of the night and more movements and awakenings than the control subjects. Further data (35, 36) suggest increased slow-wave (percent of delta wave activity) sleep in asymptomatic HIV-seropositive patients, including four patients studied again after 11 to 15 months. In a group of four CDC stage III patients, all had fragments of delta sleep in the last half of the night, which is unusual. Such alterations in sleep architecture may reflect early CNS disease in HIV-infected patients and provide a marker for prognosis or monitoring response to treatment (34). We have begun a 5-year NIMH-funded study to examine the role of elevated somnogenic cytokines in the fatigue and sleep disturbance of HIV infection. The study will involve three nights of polysomnographically recorded sleep, blood sampling throughout the night, objective testing with the Multiple Sleep Latency Test of the daytime tendency to fall asleep, computerized daytime testing of attention, continuous core temperature recording throughout the 24-hour day with an ingested temperature probe, and spectral analysis of the sleep records.

Because we did not collect data on depression in our subjects, we cannot directly assess the contributions of depression to sleepiness, fatigue, and sleep disturbance. There were group differences in early morning awakening, which would be consistent with depression. However, there were no group differences reported in difficulty falling asleep and awakenings during sleep, which are often associated with depression and may be expected if the groups differed in presence or severity of depression. Given these observations, along with our impressions from working directly with these patients, we believe that we can exclude concurrent major depression as a confounding factor in this study.

Fatigue and sleep disruption may be important features of HIV infection, have obvious implications in terms of disability and quality of life, and should be further evaluated in replications of this study, using the revised Fatigue and Sleep Questionnaire, the Stanford Sleepiness Scale, the Pittsburgh Sleep Quality Index, polysomnographically recorded sleep studies, and the Multiple Sleep Latency Test (37, 38). The importance goes beyond simplistic concepts that sick people often get tired. If the specific humoral mediators can be identified, it may be possible to treat these disabling symptoms with specific clinical interventions. This augmentation in their clinical care would be a welcome improvement to HIV-infected patients.

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# Training Directors' Opinions About the Psychiatry Resident In-Training Examination (PRITE)

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*Objective: The American College of Psychiatrists conducted research to validate the content outline of the Psychiatry Resident In-Training Examination (PRITE) and to assess what residency training directors think about the examination. Method: A mail survey was sent to the 218 psychiatry residency training directors who subscribe to the PRITE. Results: The survey response rate was 70%. A majority of the respondents indicated agreement with the relative emphasis given to each content area in the PRITE (range=52%–80% agreement). Eighty-one percent of the respondents were strongly in favor of continuing the practice of releasing the examination and the correct responses each year after the examinations have been scored. The majority of the respondents use results on the PRITE for individual resident evaluation and program evaluation (90% and 94%, respectively). Very few respondents use the PRITE results as the sole measure for assessing residents' cognitive competence or use it for marketing their residency programs. Conclusions: The survey provided strong support for the content areas covered in the PRITE and their relative emphases. The current practice of releasing PRITE items and answers (a main difference between the PRITE and the certification examination of the American Board of Psychiatry and Neurology) was well supported by the survey results. The stated purpose of the PRITE, to provide educationally useful feedback for individuals and groups in the form of comparisons with peers in specific areas of knowledge, was supported by a large majority of the respondents.*

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The popularity of in-training examinations within medical specialties has grown greatly in the past 25 years. The first written, multiple-choice in-training examination was developed in 1964 in response to concern regarding the high failure rate on the certification examination given by the American Board of Neurological Surgery. An in-training examination was developed to determine weaknesses in trainees or programs (1). Many specialty boards have seen the benefits of formative evaluation provided by in-training examinations.

The American College of Psychiatrists' Psychiatry Resident In-Training Examination (PRITE) has been administered annually since 1979 (2). The 300-item, multiple-choice examination is administered on a voluntary basis by psychiatry residency training directors who wish to provide an educational experience for their residents. More than 5,800 psychiatry residents completed the 1991 PRITE. Following the scoring of the examination, the PRITE items and correct answers are given to the residents, along with references for verification of item material. Through a comprehensive reporting system, residency training directors can also compare the performance of their residents with the performance of those in other programs. The PRITE is taken by residents in all stages of training, allowing comparison of residents to peers over time.

The American College of Psychiatrists' primary objective for the PRITE is to provide educationally useful feedback for individuals and groups in the form of comparisons with peers in specific areas of knowledge (3). The specific areas of knowledge and their relative emphases are delineated in the content outline for the examination. This outline serves as a blueprint and communicates to test users what the test measures. It also presents the content domains being measured, so that item writers can generate items that are functionally homogeneous. Content outlines should be revised periodically to ensure that they reflect changes occurring in the field over time; the process of test planning is an iterative one (4). Content outlines that are developed or updated through empirical research provide a sound starting point for the development of an examination.

The American College of Psychiatrists conducted research in consultation with American College Testing

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**TABLE 1. Preferences of 153 Residency Training Directors for Emphasis Given to Content Areas in the Content Outline of the Psychiatry Resident In-Training Examination (PRITE)**

| | Agree With Emphasis | | More Emphasis | | Less Emphasis | | No Response | |
|---|---|---|---|---|---|---|---|---|
| Content Area | N | % | N | % | N | % | N | % |
| Neurology and neurosciences | 106 | 69.3 | 25 | 16.3 | 15 | 9.8 | 7 | 4.6 |
| Psychiatry | 100 | 65.4 | 12 | 7.8 | 19 | 12.4 | 22 | 14.4 |
| Growth and development | 93 | 60.8 | 29 | 19.0 | 21 | 13.7 | 10 | 6.5 |
| Adult psychopathology | 104 | 68.0 | 32 | 20.9 | 11 | 7.2 | 6 | 3.9 |
| Emergency psychiatry | 120 | 78.4 | 18 | 11.8 | 8 | 5.2 | 7 | 4.6 |
| Behavioral science | 92 | 60.1 | 6 | 3.9 | 48 | 31.4 | 7 | 4.6 |
| Psychosocial therapies | 79 | 51.6 | 51 | 33.3 | 16 | 10.5 | 7 | 4.6 |
| Somatic treatment methods | 109 | 71.2 | 13 | 8.5 | 25 | 16.3 | 6 | 3.9 |
| Patient evaluation | 110 | 71.9 | 24 | 15.7 | 15 | 9.8 | 4 | 2.6 |
| Consultation-liaison psychiatry | 116 | 75.8 | 17 | 11.1 | 14 | 9.2 | 6 | 3.9 |
| Child psychiatry | 99 | 64.7 | 22 | 14.4 | 26 | 17.0 | 6 | 3.9 |
| Alcoholism and substance abuse | 104 | 68.0 | 12 | 7.8 | 28 | 18.3 | 9 | 5.9 |
| Miscellaneous (forensic, ethics, etc.) | 122 | 79.7 | 12 | 7.8 | 11 | 7.2 | 8 | 5.2 |

to study the current content outline for the PRITE. A confidential written survey of the 218 PRITE residency training directors was conducted to validate the outline empirically or to indicate support for changes. The results of the survey are the focus of this article.

## METHOD

The survey instrument was developed by a task force appointed by The American College of Psychiatrists in consultation with American College Testing through a series of teleconferences. The task force consisted of two members of the American Association of Directors of Psychiatry Residency Training and two members of The American College of Psychiatrists.

The current PRITE content outline is composed of two major areas: neurology and neurosciences (18%) and psychiatry (82%). The area of psychiatry contains 11 separate content domains. The primary section of the survey focused on residency training directors' preferences for the relative emphasis given to each specific content area.

In addition to collecting information regarding the PRITE content outline, the survey was designed also to assess 1) support for the practice of releasing PRITE items and answers, 2) how residency training directors use the PRITE results, 3) which textbooks are appropriate for PRITE item writing and referencing, 4) whether journals are appropriate for item writing and referencing, and 5) how programs prepare residents for the examination. In this way, the survey would provide valuable information about the PRITE that would extend beyond the issue of the validation of the content outline.

The content outline for Part I of the American Board of Psychiatry and Neurology (ABPN) examination was included in the survey instrument for comparison with the PRITE content outline. The inclusion of the content outline was authorized by the ABPN with the understanding that it would be distributed only to residency training directors subscribing to the PRITE.

One week before the survey questionnaires were mailed, each residency training director who subscribed to the PRITE was sent a letter describing the research project. The letter was intended to stimulate interest in the research and was sent from The American College of Psychiatrists with the signatures of the president of The American College of Psychiatrists and the PRITE editor-in-chief. The survey instruments were mailed by The American College of Psychiatrists in October 1990. Return envelopes addressed to American College Testing were included. The survey questionnaires were coded to facilitate follow-up correspondence with nonrespondents.

By mid-November 1990, American College Testing had received 94 responses to the survey, a 43% response rate. A second copy of the survey questionnaire with a letter and return envelope was mailed by American College Testing to the 124 residency training directors whose materials had not been received. The letter included directions to disregard the second copy if the two copies had crossed in the mail.

A total of 153 responses were received, which corresponds to a 70% response rate for the study. Survey instruments received after Dec. 7, 1990, were not included in the data analysis. Late responses did not differ significantly from those received on time.

A 70% response rate is considered quite good for written survey research. The American College of Psychiatrists did not feel that it was necessary to encourage further the training directors who had not yet responded, as nonresponding programs were not systematically different from responding programs.

## RESULTS

The results of the survey showed strong support for the current PRITE content outline. A majority of the respondents indicated agreement with the relative emphasis given to each content area, and a majority did not indicate any content areas that should be added or deleted. The preferences of survey respondents are shown in table 1. The percentages of respondents indicating agreement ranged from 51.6% to 79.7% for the various content areas.

Only 23 respondents (15.0%) indicated additional areas that should be included in the PRITE content outline. Geriatric psychiatry was listed by eight respondents; the other areas indicated were varied. Only nine respondents (5.9%) indicated content areas for deletion; these areas also were varied.

The residency training directors were asked to indicate their feelings about maintaining the educational aspect of the PRITE by releasing the examination and correct responses each year. This represents the major difference between the PRITE (as an educational tool) and Part I of the ABPN certification examination. A 5-point Likert-type rating scale was used for responses: 5=strongly in favor of and 1=strongly opposed to releasing PRITE items and answers to residents. The mean of the ratings was 4.65. Eighty-one percent (N=124) of the respondents were strongly in favor of maintaining the educational aspect of the PRITE by releasing the examination and correct responses each year; no respondents were strongly opposed.

On the item asking whether they would be in favor of *stopping* the practice of releasing the PRITE items and answers to establish greater similarity to Part I of the ABPN examination, 7.2% (N=11) of the respondents answered yes and 89.5% (N=137) answered no (3.3%, N=5, did not answer). It is interesting to note that this question elicited the greatest consensus within the survey.

The residency training directors were asked to respond to a list of possible uses that could be made of PRITE results by indicating the ones applicable to their programs. The majority of the respondents indicated more than one use, most frequently choosing the categories of program evaluation and individual resident evaluation (table 2).

The training directors were also asked to indicate any additional uses of PRITE results that their programs make. Additional uses were indicated by 21 respondents (13.7%). Counseling of residents was listed by eight respondents, and practice for the ABPN examination was listed by seven. The other uses were varied.

In the comparison of the ABPN Part I content outline and the PRITE content outline, about one-half of the respondents could see advantages in using the ABPN Part I content outline for the PRITE, and about one-half could see disadvantages in doing so. With respect to advantages, 45.8% (N=70) could not see any advantages, while 49.0% (N=75) indicated that they could see advantages (5.2%, N=8, did not respond to this item). Explanations of advantages were listed by 72 respondents. Almost one-half of these indicated an element of practice/preparation for the ABPN Part I examination, and approximately one-third indicated a preference for some content area or the total format of the ABPN content outline rather than the one used for the PRITE. Several respondents listed the possibility of better predictive power of results on the ABPN Part I examination; other responses were varied.

With respect to the disadvantages of using the ABPN Part I content outline, 43.8% (N=67) of the respondents indicated that they did not see any disadvantages, while 45.8% (N=70) indicated that they saw disadvantages (10.5%, N=16, did not respond to this item). Explanations of disadvantages were listed by 68 respondents. More than one-half of these respondents indicated that neurology was given too much emphasis in the ABPN Part I content outline to be appropriate for the PRITE. Approximately one-fourth indicated a preference for maintaining child psychiatry and consultation-liaison psychiatry as separate content areas. Several respondents listed a more global indication of preference for the PRITE content outline; other responses were varied.

**TABLE 2. Responses of 153 Residency Training Directors Regarding Use of Results on the Psychiatry Resident In-Training Examination (PRITE)**

| Use | N | %[a] |
|---|---|---|
| Program evaluation | | |
| Comparing program's mean scores to the national percentiles | 142 | 92.8 |
| Evaluating specific content areas to identify program strengths and weaknesses | 144 | 94.1 |
| Modifying curriculum | 116 | 75.8 |
| Individual resident evaluation | | |
| Identifying residents' weaknesses so as to focus future training better | 138 | 90.2 |
| Use in conjunction with other measures for assessing residents' cognitive competence so as to determine progress in training | 102 | 66.7 |
| Use as sole measure for assessing residents' cognitive competence so as to determine progress in training | 2 | 1.3 |
| Marketing residency program (distributing program results to residency applicants) | 8 | 5.2 |

[a] Percentages do not total 100 because respondents were directed to select as many categories as applied to their programs.

The texts currently in the PRITE library that are available to writers and reviewers of PRITE items were listed in the survey instrument. Training directors were asked to check "yes" for each text they recommended to be used for the PRITE and "no" for each text they did not recommend. The majority of respondents indicated support for nearly all of the texts. There were no texts for which the majority of respondents indicated "no." A higher percentage of nonresponse was seen for this section of the survey, possibly indicating that some respondents were not comfortable evaluating all the texts listed.

For the question about whether or not journal articles should be used for PRITE item writing and referencing, 69.3% (N=106) indicated yes, and 28.1% (N=43) indicated that journals should not be used (2.6%, N=4, did not respond).

The training directors were asked to indicate, on a list of possible approaches to preparing residents for the PRITE, the ones that were applicable to their programs. A majority of the respondents indicated that no specific recommendations are given to residents. The percentages of respondents who selected each approach are presented in table 3.

In response to the item asking whether all programs should be required to adopt uniform practices to pre-

**TABLE 3. Approaches Taken by 153 Residency Training Directors to Prepare Residents for the Psychiatry Resident In-Training Examination (PRITE)**

| Approach | N | %[a] |
|---|---|---|
| No specific recommendations are given to residents | 90 | 58.8 |
| Residents are encouraged to take the examination without any preparation | 46 | 30.1 |
| Residents are encouraged to study for the examination | 29 | 19.0 |
| Residents are encouraged to form study groups | 12 | 7.8 |
| Study sessions are scheduled for residents | 8 | 5.2 |
| Practice examinations are administered to residents | 5 | 3.3 |
| Residents are relieved of on-call responsibilities in order to prepare for the examination | 8 | 5.2 |

[a] Percentages do not total 100 because respondents were directed to select as many categories as applied to their programs.

pare residents to take the PRITE, 79.7% (N=122) of the respondents indicated no, and 17.6% (N=27) indicated yes (2.6%, N=4, did not answer). Several respondents included an unsolicited comment indicating that enforcement of uniformity would be problematic.

## DISCUSSION

A majority of the residency training directors indicated agreement with the relative emphasis given to each content area of the PRITE, and only a small percentage of respondents listed content areas that should be added or deleted. There was strong support for continuing the practice of releasing the examination and the correct responses. It is this practice that clearly differentiates the in-training examination from the next examination in the career path, the certification examination. Residency training directors indicated that they use PRITE results for program evaluation and individual resident evaluation. Only very small percentages indicated that they use PRITE results for marketing a residency program or as the sole measure for assessing residents' cognitive competence so as to determine progress in training.

The responses also indicated that the hypothetical question regarding the appropriateness of adopting the ABPN Part I content outline for the PRITE is a complex issue. About one-half of the residency training directors saw advantages for doing so, and one-half saw disadvantages. Key areas for comparison of the two tests' content outlines are the emphasis given to neurology and neurosciences and the distribution of items in the areas of child psychiatry and consultation-liaison psychiatry. Regarding the current PRITE content outline, 69.3% of the respondents indicated that neurology and neurosciences should continue to be given a relative emphasis of 18% on the test. Many of the respondents who listed disadvantages of adopting the ABPN Part I content outline for the PRITE indicated that the outline gave too much emphasis to neurology and neuropsychiatry. Many respondents indicated that the current curriculum for residents must be reflected in the PRITE.

The percentages of respondents indicating agreement with the relative emphasis given to child psychiatry and consultation-liaison psychiatry in the current PRITE content outline were 64.7% and 75.8%, respectively. Many respondents who listed disadvantages for adopting the ABPN Part I content outline for the PRITE indicated that these content areas should remain as distinct areas, with scores reported.

The most common advantage indicated for adopting the ABPN Part I content outline for the PRITE was the element of practice or preparation for the ABPN examination. This was slightly confounded by other responses indicating that the PRITE is currently used as practice/preparation for the ABPN examination. Several respondents noted that the predictive validity of the PRITE for the ABPN examination would be one advantage in adopting the ABPN Part I content outline for the PRITE. The American College of Psychiatrists will pursue research to establish the relation between performance on the PRITE (with its current content outline) and performance on the ABPN Part I examination. It may be shown that evidence of predictive validity is already at a level sufficient for counseling residents.

The majority of the texts used for writing and referencing PRITE items were supported in the survey. The use of journals for writing and referencing PRITE items was also supported in the survey results.

A majority of the respondents indicated that no specific recommendations are given to residents preparing for the PRITE. Only small percentages of respondents actively prepare residents by scheduling study sessions, administering practice examinations, or relieving residents of on-call responsibilities. A majority of the training directors indicated that uniform practices in preparing residents for the PRITE should not be required. It appears that residency training directors are using the approaches that work best for their programs and would prefer not to have practices mandated.

Overall, the survey results provided strong support for the content areas covered in the PRITE and their relative emphases. The current practice of releasing PRITE items and answers was also well supported by the survey results. It appears that The American College of Psychiatrists' purpose for the PRITE, to provide educationally useful feedback for individuals and groups in the form of comparisons with peers in specific areas of knowledge, is supported by a large majority of the psychiatry residency training directors who subscribe to the PRITE.

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# Late Luteal Phase Dysphoric Disorder in 670 Women Evaluated for Premenstrual Complaints

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*Objective: The American Psychiatric Association's DSM-IV Work Group on Late Luteal Phase Dysphoric Disorder (LLPDD) reanalyzed existing data from prospective, daily symptom ratings to evaluate the* DSM-III-R *criteria for LLPDD. The objectives were to 1) evaluate the individual symptoms presently required for the diagnosis and other symptoms, 2) determine the proportion of treatment-seeking women who meet the LLPDD criteria, and 3) explore the association between LLPDD and other mental disorders. Method: Data from over 1,000 women seeking evaluation for premenstrual complaints at five U.S. sites were examined. The data from 670 of these women were sufficiently complete to warrant evaluation by four different methods of assessing symptom change. Results: Depending on the assessment method used, 14% to 45% of the women met the criteria for LLPDD. The current* DSM-III-R *symptoms were classified as positive for 7% to 54% of the women. Each of these symptoms was significantly more common among women with LLPDD regardless of the assessment method used. Five symptoms not presently included were also significantly more common. Women who had had mental disorders in the past, but not present, showed a significantly greater, but very small, relative risk of LLPDD. Conclusions: The variability in the frequency of LLPDD diagnosis according to method of assessing symptom change underscores the need for a uniform assessment method. The five additional symptoms with frequencies comparable to those of the* DSM-III-R *symptoms should be studied further for possible inclusion in the criteria.*
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Late luteal phase dysphoric disorder (LLPDD), as defined in *DSM-III-R*, is a subset of premenstrual syndrome (PMS). Women with LLPDD suffer primarily from severe mood symptoms that repeatedly occur in the luteal phase of the menstrual cycle. After reviewing the literature on PMS and LLPDD (1–10), the American Psychiatric Association's DSM-IV Work Group on Late Luteal Phase Dysphoric Disorder concluded that empirical justification of procedures for identifying a homogeneous group of women with the disorder was needed, as was some understanding of the relationship between LLPDD and other mental disorders. Therefore, the work group, in conjunction with the Task Force on DSM-IV, authorized a reanalysis of existing primary data from women seeking evaluation for premenstrual complaints.

LLPDD differs from other diagnoses in *DSM-III-R* because it requires the documentation of symptom change by prospective, daily records. Unfortunately, *DSM-III-R* does not specify how to compute the change, nor do researchers agree about how best to do so (11). The work group decided, therefore, to compare four existing methods that represented a range of simple to complex approaches.

The objectives of the database analysis were 1) to evaluate the individual symptoms presently required for the diagnosis and other symptoms, 2) to determine the proportion of women who met the LLPDD criteria, and 3) to explore the association between LLPDD and other mental disorders. We addressed them by first determining the percentage of women whose late luteal phase symptoms satisfied the four different change criteria. We then examined the association between the diagnosis and in-

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**TABLE 1. *DSM-III-R* LLPDD Symptoms and Corresponding Symptoms From Rating Scales Used in Five Studies**

| *DSM-III-R* LLPDD Symptoms | Original Rating Scale Symptoms |
|---|---|
| Marked affective lability | Mood swings, feel labile<br>Rapid changes in mood |
| Persistent and marked anger or irritablity | Irritability, anger, temper, or impatience |
| Marked anxiety, tension | Anxious, jittery, nervous<br>Nervous tension<br>Feel under stress |
| Markedly depressed mood | Depressed, sad, low, blue, tearful, or lonely |
| Decreased interest in usual activities | Loss of interest or pleasure in usual activities<br>Avoid social activities |
| Easy fatigability or marked lack of energy | Low or decreased energy, fatigue, feel unable to move, tired or weak |
| Subjective sense of difficulty in concentrating | Distractible, difficulty concentrating<br>Confusion<br>More forgetful |
| Marked change in appetite or food cravings | Decreased appetite<br>Increased appetite<br>Craving foods |
| Hypersomnia or insomnia | Decreased or increased sleep, insomnia<br>More sleep, naps, stay in bed |
| Physical symptoms | Headaches<br>Breast tenderness, swelling, or pain<br>Abdominal bloating, swelling, pain, or heaviness<br>Back, joint, or muscle pain or aches<br>Feel bloated, have edema |

dividual symptoms, including the 10 LLPDD symptoms and 21 others. We also computed the relative risk of LLPDD as a function of psychiatric history.

The work group's approach to these questions was unique in its use of existing primary data from several cooperating investigators. This cooperation allowed us to directly compare symptom formats, methods of evaluating symptom change, and the association of psychiatric disorder history with a diagnosis of LLPDD.

## METHOD

### *Subjects*

The subjects for the present investigation were drawn from five PMS clinics associated with university and/or large urban hospitals in the eastern United States. Site selection was based on the availability and accessibility of data and the subjects' willingness to participate. Women at all sites were both recruited by advertisement and seen as patients seeking evaluation and treatment of premenstrual difficulties.

The original pool of 1,089 women rated their symptoms daily, providing data on 2,106 menstrual cycles. To minimize the inclusion of anovulatory cycles, only cycles between 22 and 35 days in length (mean=26.9, SD=4.0) were included (12). Women with symptom ratings for fewer than two complete menstrual cycles each or whose mental histories were not available were also excluded. The remaining 670 women can be summarized as follows: mean age=34 years (SD=5.6), percent of white subjects=95%, percent employed at least part-time=69%, percent with at least some college education=78%. These women reported an average of 1.3 children (SD=1.2), 1.9 pregnancies (SD=1.6), and a duration of premenstrual symptoms of 7.6 years (SD=6.7). Compared to the general U.S. population of women, this group was equally likely to be employed, was better educated, and had fewer children.

### *Measures*

At four sites data on lifetime mental history were collected by using structured interviews. At three sites the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (13) was used and psychiatric diagnoses were made with the Research Diagnostic Criteria (14). At one site the Diagnostic Interview Schedule (15) was used and psychiatric diagnoses were made with the *DSM-III* criteria. At the remaining site a clinical interview was used and diagnoses were made with *DSM-III* criteria.

Each site used its own symptom rating form. The women were asked to rate from 17 to 33 symptoms daily. Items with content that was identical or very similar to the symptoms of LLPDD were selected to evaluate the presence or absence of these symptoms. The LLPDD symptoms and their relationship to the original items are shown in table 1.

Ratings were typically made on a 6-point rating scale on which each scale point was labeled to reflect the intensity of the symptom compared to the woman's symptom-free state. Symptoms were assessed by using four different procedures. Three procedures compared symptom ratings during follicular phase days 5–10 (where day 1 is the first day of menses) and the last 6 days of the luteal phase. These days were selected to avoid symptoms associated with menses or ovulation, to be of equal length, and to address criterion A of LLPDD, which requires the presence of symptoms "during the last week of the luteal phase" and remission of symptoms "within a few days after the onset of the follicular phase." The absolute severity method (16) required follicular phase ratings of no more than minimal (a rating of 2) for at least 4 of the 6 follicular phase days and a severe or extreme rating (a rating of 5 or 6) for at least 1 late luteal phase day. The percent change method (16) required mean late luteal phase severity to exceed by at least 75% mean follicular phase severity. The effect size method (17) required mean late luteal phase severity to exceed mean follicular phase symptom severity by at least the standard deviation of scores for that symptom in that cycle. The trend analysis method (18) defined a symptom as present if the exponentially forecasted severity score was significantly increased ($p<0.05$) on at least 1 day during the last 2 weeks of the cycle and was significantly decreased any time after cycle day 7 but not after the beginning of the increase.

An LLPDD diagnosis for each method required a

**TABLE 2. Frequency of *DSM-III-R* LLPDD Symptoms in 670 Women With Premenstrual Complaints, According to Four Methods of Assessing Symptom Change**[a]

| | Frequency Among All Women Studied | | | | | | | | Frequency Among Women With LLPDD Diagnoses Based on Four Assessment Methods | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Absolute Severity | | Effect Size | | Percent Change | | Trend Analysis | | Absolute Severity (N=95) | | Effect Size (N=253) | | Percent Change (N=229) | | Trend Analysis (N=304) | |
| LLPDD Symptom | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Marked affective lability | 80 | 12 | 198 | 30 | 180 | 27 | 255 | 38 | 52 | 55 | 166 | 66 | 151 | 66 | 218 | 72 |
| Persistent and marked anger or irritability | 71 | 11 | 239 | 36 | 219 | 33 | 247 | 37 | 38 | 40 | 186 | 74 | 159 | 69 | 201 | 66 |
| Marked anxiety, tension | 93 | 14 | 235 | 35 | 200 | 30 | 255 | 38 | 53 | 56 | 184 | 73 | 157 | 69 | 210 | 69 |
| Markedly depressed mood | 107 | 16 | 291 | 43 | 269 | 40 | 360 | 54 | 48 | 50 | 181 | 72 | 159 | 69 | 248 | 82 |
| Decreased interest in usual activities | 95 | 14 | 275 | 41 | 261 | 39 | 292 | 44 | 49 | 52 | 172 | 68 | 155 | 68 | 208 | 68 |
| Easy fatigability or marked lack of energy | 44 | 7 | 99 | 15 | 94 | 14 | 151 | 23 | 23 | 24 | 75 | 30 | 68 | 30 | 114 | 38 |
| Subjective sense of difficulty in concentrating | 117 | 18 | 246 | 37 | 234 | 35 | 304 | 45 | 66 | 70 | 176 | 70 | 169 | 74 | 216 | 71 |
| Marked change in appetite or food cravings | 92 | 14 | 190 | 28 | 174 | 26 | 252 | 38 | 49 | 52 | 147 | 58 | 132 | 58 | 189 | 62 |
| Hypersomnia or insomnia | 106 | 16 | 228 | 34 | 202 | 20 | 256 | 38 | 67 | 71 | 176 | 70 | 159 | 69 | 219 | 72 |
| Physical symptoms | 68 | 10 | 261 | 24 | 142 | 21 | 188 | 28 | 41 | 43 | 117 | 46 | 93 | 41 | 129 | 42 |

[a]See text for explanations of the four methods.

positive classification of at least five of the 10 symptoms—at least one of which was anxiety, depression, irritability, or mood lability—in two or more cycles. For compound symptoms (e.g., hypersomnia or insomnia), the symptom was considered present if any of the possibilities was present. This approach to assessing multiple cycles for the same woman reflects criterion E of LLPDD, which requires that symptoms be "confirmed by prospective daily self-ratings during at least two symptomatic cycles."

## RESULTS

The number of women who received diagnoses of LLPDD varied with the method used to assess symptom change. The absolute severity method produced the fewest number of women with diagnoses of LLPDD (N=95, 14%) and the lowest percentages of positive symptoms regardless of LLPDD diagnosis (7% to 18% of all women). The trend analysis method produced the largest number of women with diagnoses of LLPDD (N=304, 45%) and the highest percentages of positive symptoms regardless of LLPDD diagnosis (23% to 54% of all women). The effect size and percent change methods produced intermediate numbers of LLPDD diagnoses (N=253, 38%, and N=229, 34%, respectively) and percentages of women with positive symptoms (15% to 43% of all women and 14% to 40% of all women, respectively).

The frequency of occurrence of the 10 symptoms of LLPDD is shown in table 2. Individual symptoms were classified as positive for as few as 7% of the women and as many as 54%, depending on the symptom and assessment method used. Significantly more women diagnosed with LLPDD than women without LLPDD had positive LLPDD symptoms ($\chi^2$=56.2–270.3, df=1, p< 0.0001). For example, a subjective sense of difficulty in concentrating was found in at least 70% of the women with LLPDD, regardless of assessment method, and in as few as 9% of the women without diagnoses of LLPDD. Other symptoms—for example, easy fatigability or marked lack of energy—although found relatively infrequently in women without LLPDD, were also found relatively infrequently in women with LLPDD. Averaged across the four methods, sleep disturbance and concentration difficulties were the most common symptoms among the women with LLPDD and fatigability was the least common. Averaged across all four assessment methods, the proportion of subjects who had at least one positive symptom each was four times as high among the women with LLPDD (60%) as among the women without LLPDD (14%).

A total of 21 additional symptoms were rated by women from one or more of the sites. On average, the number of women who indicated premenstrual exacerbations of these symptoms was one-quarter to one-third the number who indicated symptoms of LLPDD. However, five of these 21 symptoms were assessed positively with all four methods approximately as frequently as the 10 LLPDD symptoms and with significant differences in frequency of occurrence between women with LLPDD and women without LLPDD ($\chi^2$=16.0–133.5, df=1, p<0.001). Data for these five symptoms are shown in table 3.

Nearly three-quarters of the 670 women, who were not prescreened for mental disorders, either never met criteria for any mental disorder (N=223, 33%) or met criteria for mental disorders only in the past (N=264, 39%). Among the women who met criteria for mental disorders only in the past, an average of 1.5 mental disorders (SD=0.7) was recorded. The criteria for a present

**TABLE 3. Frequency of Five Additional Symptoms in 670 Women With Premenstrual Complaints, According to Four Methods of Assessing Symptom Change[a]**

| Symptom (and number of women who rated symptom) | Frequency Among All Women Who Rated Symptom | | | | | | | | Frequency Among Women With LLPDD Diagnoses Based on Four Assessment Methods[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Absolute Severity | | Effect Size | | Percent Change | | Trend Analysis | | Absolute Severity | | Effect Size | | Percent Change | | Trend Analysis | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Intense reaction to daily events (N=85) | 18 | 21 | 22 | 26 | 22 | 26 | 10 | 12 | 17 | 71 | 17 | 49 | 19 | 51 | 6 | 50 |
| Decreased self-esteem (N=85) | 15 | 18 | 26 | 31 | 26 | 31 | 6 | 7 | 13 | 54 | 22 | 63 | 22 | 59 | 6 | 50 |
| Gloomy, pessimistic, despondent (N=85) | 15 | 18 | 25 | 31 | 26 | 31 | 9 | 11 | 12 | 50 | 23 | 66 | 24 | 65 | 7 | 58 |
| Less desire to move, talk (N=183) | 24 | 13 | 48 | 26 | 44 | 24 | 70 | 38 | 14 | 74 | 33 | 66 | 31 | 74 | 42 | 71 |
| Problems coping, out of control, feel overwhelmed (N=526) | 59 | 11 | 135 | 26 | 133 | 25 | 180 | 34 | 37 | 51 | 111 | 52 | 104 | 54 | 140 | 58 |

[a] See text for explanations of the four methods.

[b] Percent based on number of subjects with LLPDD diagnosis who rated the particular symptom.

history of mental disorder were met by 27% of the women (N=183). Slightly more than one-half of these women (59%) also met the criteria for a past history of mental disorder. Among all women with present histories, averages of 1.4 present disorders (SD=0.7) and 0.9 past disorders (SD=1.0) were recorded.

Significantly more of the women with only past histories of mental disorders were diagnosed with major depressive disorder than were women with present histories of mental disorders (61% versus 29%; $\chi^2$=44.2, df=1, p<0.001). Significantly more of the women with present mental disorders, compared to the women with only past histories, were diagnosed with depressive disorders other than major depressive disorder (51% versus 32%; $\chi^2$=14.9, df=1, p<0.001), with phobia (36% versus 5%; $\chi^2$=72.4, df=1, p<0.001), and with other disorders, including substance abuse, psychotic disorders, and personality disorders (44% versus 27%; $\chi^2$=12.9, df=1, p<0.001).

Relative risk estimates were used to compare the frequencies of LLPDD diagnoses in the groups with mental disorders in the past only and in the present with the frequency in the group with no mental disorders. For the group with histories of mental disorders in the past only, the relative risk of a diagnosis of LLPDD averaged 1.14. This indicates that in this group of women who sought help for premenstrual complaints, women with past histories of mental disorders had a 14% greater chance of being diagnosed with LLPDD than women with no history of mental disorders. As shown in table 4, all methods except the absolute severity method showed a significantly greater risk of LLPDD in women with past psychiatric histories only.

In contrast, a present history of a mental disorder did not increase the relative risk of receiving an LLPDD diagnosis regardless of assessment method (see table 4). Averaged over the four methods, the relative risk of being diagnosed with LLPDD for the group with present mental disorders was 0.92.

To determine if the greater risk of LLPDD in the group with mental disorders in the past only was due to their greater likelihood of having major depressive disorder, we examined the risk of LLPDD as a function of past-only or current major depressive disorder relative to no disorder. Risk was not significantly increased for women with past major depressive disorder only except when LLPDD was diagnosed by trend analysis (relative risk=1.32, 95% confidence interval=1.07–1.62, p<0.01). The relative risks for the absolute severity, effect size, and percent change methods were 0.74, 1.20, and 1.28, respectively (lowest p=0.13).

## DISCUSSION

These data demonstrate that the percentage of women evaluated for premenstrual complaints who receive the diagnosis of LLPDD varies from 14% to 45%, depending on the method chosen for evaluating changes in symptom severity. Among these women, the LLPDD symptoms, and relatively few others, were documented in significantly more women with LLPDD than women without LLPDD. Because only five of the 10 *DSM-III-R* symptoms were required for a diagnosis, it was predictable that no single symptom would be especially frequent among the women with LLPDD diagnoses. Among the additional 21 symptoms evaluated, five symptoms with frequencies comparable to those of the *DSM-III-R* symptoms were found. The content of four of these items is close to that of specific LLPDD symptoms, and their presence or absence was significantly related to these symptoms. The item "intense reaction to daily events" was associated with the LLPDD symptoms "marked affective lability" (kappa=0.70), and the items "decreased self-esteem" and "feeling gloomy, pessimistic, despondent" were closely related to the LLPDD symptom "markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts" (kappa=0.62 for both). "Less desire to move, talk" was associated with the LLPDD symptom "easy fatigability or marked lack of energy" (kappa=0.68). Finally, "problems coping, out of control, feel overwhelmed" may relate to LLPDD criterion C, which involves the severity of a premenstrual disturbance: "seriously interferes

**TABLE 4. Relative Risk of an LLPDD Diagnosis as a Function of Lifetime History of Psychiatric Disorders in 670 Women With Premenstrual Complaints**

| Method of Assessing Symptom Change[a] | Prevalence of LLPDD (%) in Women With No Psychiatric History (N=223) | Lifetime Psychiatric History in Past Only (N=264) | | | Lifetime Psychiatric History in Present (N=183)[b] | | |
|---|---|---|---|---|---|---|---|
| | | Prevalence of LLPDD (%) | Relative Risk | 95% Confidence Interval | Prevalence of LLPDD (%) | Relative Risk | 95% Confidence Interval |
| Absolute severity | 17 | 13 | 0.80 | 0.52–1.22 | 13 | 0.76 | 0.47-1.22 |
| Effect size | 34 | 43 | 1.25[c] | 1.00–1.57 | 34 | 0.98 | 0.75–1.29 |
| Percent change | 30 | 39 | 1.29[d] | 1.01–1.65 | 31 | 1.02 | 0.76–1.37 |
| Trend analysis | 43 | 52 | 1.23[e] | 1.02–1.48 | 39 | 0.91 | 0.72–1.15 |

[a] See text for explanations of the four methods.
[b] Fifty-nine percent of these women also had past histories of mental disorders.
[c] $\chi^2=3.79$, df=1, $p<0.05$ (Mantel-Haenszel chi-square).
[d] $\chi^2=4.18$, df=1, $p<0.05$ (Mantel-Haenszel chi-square).
[e] $\chi^2=4.52$, df=1, $p<0.05$ (Mantel-Haenszel chi-square).

with work or with usual social activities or relationships with others." These five symptoms should be studied further for possible inclusion among the diagnostic criteria.

The weak association between major depressive disorder and LLPDD raises questions about previous reports of a higher than average likelihood of affective disorder among women with premenstrual complaints (19). Although the relative risks based on effect size and percent change diagnoses were not statistically significant, their magnitude was similar to the statistically significant estimate for trend analysis, suggesting a possible type II error. Even so, the higher risk of LLPDD among women with major depressive disorder in the past was slight when the women were diagnosed with the trend analysis, effect size, and percent change methods, and the risk was actually lower than for women with no psychiatric history when the women were diagnosed by the absolute severity method, which employed the strictest diagnostic criteria. These data demonstrate that the diagnosis of LLPDD is not merely synonymous with a diagnosis of another mental disorder or more likely among women with affective disorders when explicit criteria for late luteal phase severity and early follicular phase remission are used. Moreover, among these subjects, at least one in six of the women with no past or present mental disorders met the most stringent symptom definition of LLPDD.

We were not able to address the relationship between LLPDD and other mental disorders in sufficient detail to fulfill the LLPDD requirement that the symptoms of LLPDD not be "merely an exacerbation of the symptoms of another disorder." This would require data on the relative times of onset of these disorders and their symptom profiles, which were unavailable to us. However, at least one attempt has been made to separate symptoms of mental disorders that are exacerbated by the late luteal phase from other symptoms (20). Additional attempts to do so should be encouraged in order to determine the actual prevalence of LLPDD among women with past or present histories of mental disorders.

Using any of the assessment methods, we failed to confirm a pattern of symptom exacerbation related to menstrual cycle phase in one-third of the women. Since these data were provided by women who sought help for premenstrual complaints, we believe that a rigorous application of the full criteria for the disorder would make it difficult to confuse this diagnosis with minor symptomatic complaints associated with the menstrual cycle. These figures most likely represent an overestimate of LLPDD's frequency of occurrence in the general population and should not be generalized to reflect the prevalence of LLPDD among all women.

## CONCLUSIONS

Between 14% and 45% of the treatment-seeking women in this study met the *DSM-III-R* criteria for LLPDD. This variability in the frequency of occurrence of the diagnosis of LLPDD has been observed by others (11, 21) and underscores the need for researchers to use a uniform method for evaluating symptom change. These frequency estimates should not be used as prevalence estimates for LLPDD because they are based on a secondary analysis of previously existing data sets that were similar but not identical and involve primarily treatment-seeking subjects. Furthermore, the five sites from which these data were drawn may not adequately represent the various types of settings in which women with premenstrual complaints seek treatment. We recommend the systematic collection of data from representative sites with the same semistructured interview to determine the provisional diagnosis of LLPDD, the diagnosis of other mental disorders, and the age at onset for each. Such a study should also include the prospective evaluation of the LLPDD symptoms plus the additional five symptoms not directly represented among the existing criteria, in particular, the symptom "problems coping, out of control, feel overwhelmed." Given the better performance of the item "less desire to move, talk" than of "easy fatigability or marked lack of energy," consideration should be given to rewording this criterion for LLPDD.

We recommend the absolute severity method for determining symptom change since it ensures an asymptomatic follicular phase and a severely symptomatic late luteal phase. This method is the most conservative of the methods examined here and the easiest to apply clinically. No mathematical treatment of the prospective ratings is required, and an evaluation of the LLPDD criteria can be carried out by simple inspection of a plot of the daily ratings. For research purposes, however, an approach that combines absolute severity criteria with consideration of the variability in symptom severity throughout the entire menstrual cycle, such as the effect size method, would be preferable. This would allow investigators to assess changes in LLPDD severity (e.g., due to treatment or across cycles) and to compare their results with the results of investigators from different sites.

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# Course of Premenstrual Syndrome Symptom Severity After Treatment

Ellen W. Freeman, Ph.D., Karl Rickels, M.D., and Steven J. Sondheimer, M.D.

*Objective: Patients from a randomized, double-blind, placebo-controlled study of progesterone suppository treatment for premenstrual syndrome (PMS) were followed up to determine poststudy PMS symptom levels and medication use. Method: An average of 1 year after the end of the treatment study, 129 subjects were contacted for telephone interviews. All subjects met criteria for PMS before the progesterone suppository treatment, and their symptoms were confirmed by daily symptom reports throughout the study. The outcome measure at follow-up was the patient's global assessment of symptom severity, which was also rated by the subjects during the treatment study. The ratings at enrollment, end of study, and follow-up were compared. Results: Only 27% of the subjects (N=35) were taking medications for PMS at follow-up. Symptom severity at follow-up was less than at enrollment but greater than at the end of the study. Conclusions: Some of the improvement gained during treatment was maintained, but overall the subjects remained moderately symptomatic. Validation of the PMS condition, education, and support and caring may account for the symptom decreases during treatment, and the end of treatment and withdrawal of these conditions may account for the moderate return of symptoms.*

(Am J Psychiatry 1992; 149:531–533)

Treatment of premenstrual syndrome (PMS) (provisionally termed "late luteal phase dysphoric disorder" in *DSM-III-R*) often results in symptom reduction, even when active medication is no more effective than placebo (1–3). However, to our knowledge there have been no follow-up reports of PMS patients to describe the course of symptoms after medical intervention. Improvement experienced during treatment could be due to numerous psychological factors affecting patient expectations and could have long-term as well as transitory effects (4).

We conducted a follow-up study of extensively evaluated PMS subjects who participated in an 8-month treatment protocol. In the double-blind, placebo-controlled crossover treatment study (5), there was significant symptom reduction from baseline but no statistically significant difference between the medication and placebo. Follow-up was conducted to determine symptom levels during the most recent menstrual cycle and to learn whether the subjects had continued to take their medications for PMS.

## METHOD

### *Subjects*

The 168 subjects in the original study were extensively evaluated and met criteria for PMS before their progesterone suppository treatment (5). The study staff contacted 129 (77%) of them for telephone interviews an average of 1 year after the end of the study. The other 39 subjects could not be located. There were no differences between the contacted and noncontacted subjects in comparisons of study variables that included medical history, background characteristics, and premenstrual symptom score (from daily reports) at the end of the study.

The subjects met the following criteria before random assignment to treatment in the initial study: 1) moderate to severe symptoms in the premenstrual week with relief after the onset of menses, 2) an increase of at least 50% in the total premenstrual symptom score (days 22–28) over postmenstrual score (days 6–12), based on the subjects' daily symptom reports (description to fol-

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**TABLE 1. PMS Symptom Severity of 129 Women at Beginning of Treatment Study, End of Study, and Follow-Up**[a]

| | PMS Symptom Severity in Most Recent Menstrual Cycle (0=none, 4=extreme) | | | |
|---|---|---|---|---|
| | Follow-Up Less Than 12 Months (mean=6 months) (N=84) | | Follow-Up 12 Months or More (mean=18 months) (N=45) | |
| Time | Mean | SD | Mean | SD |
| Enrollment in study | 2.86 | 0.98 | 2.95 | 0.94 |
| End of study | 1.81 | 1.35 | 1.71 | 1.34 |
| Follow-up | 2.24 | 1.12 | 2.33 | 1.23 |

[a] ANOVA multivariate tests showed significant main effect of time (F=40.5, df=2, 124, p<0.0001) but nonsignificant main effect of group (F=0.03, df=1, 125) and interaction of time and group (F=0.14, df=2, 124). All between-time comparisons showed significant differences (p<0.05, pairwise t tests).

low), 3) low symptom score during the follicular phase, 4) no current major psychiatric diagnosis as determined by structured diagnostic interview using a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (6) and *DSM-III* criteria, 5) occurrence of PMS in most cycles during the past year according to subject report, and 6) confirmation of symptom status by daily symptom reports after a four-cycle evaluation period including two cycles of pill-placebo washout. These criteria met the National Institute of Mental Health guidelines for PMS (7). Most subjects also met the criteria for late luteal phase dysphoric disorder in *DSM-III-R,* which was published while this study was in progress.

### *Symptom Assessments*

Symptoms were assessed through the daily symptom reports maintained by the subjects throughout the eight-cycle study. The report form listed 17 symptoms that are associated with PMS and have been included in diaries used in previous PMS studies (8–10): nervous tension, mood swings, irritability, anxiety, loss of control, fatigue, depression, crying, insomnia, swelling, breast tenderness, headache, food cravings, confusion, poor coordination, aches, and cramps. The subjects rated each symptom daily from 0 (not at all) to 4 (severe). The scores were summed for a daily total score.

The outcome measure at follow-up was the patient's global assessment of symptom severity. The subjects were asked to indicate the overall severity of their symptoms (0=none, 4=extreme) during the most recent premenstrual time. During the treatment study, the subjects completed the same global assessment at enrollment and at the end of the study, and those results were consistent with the daily symptom scores, which were used as the primary outcome variable in the treatment study. The Pearson coefficient of correlation between the global severity scores and the daily symptom ratings at the end of the study was r=0.56 (p<0.0001). In the follow-up investigation, the severity scores at the three time points (enrollment, end of study, and follow-up) were analyzed by using repeated measures analysis of variance (ANOVA) with least squares means and paired t tests in post hoc pairwise comparisons.

## RESULTS

At follow-up, only 27% of the 129 subjects (N=35) were taking medications for PMS; the majority of this group (N=22) were using progesterone, which was prescribed for subjects who wished to continue to take it after the study. The other medications included nonsteroidal analgesics (N=5), vitamins (N=5), and anxiolytics (N=3). The mean symptom severity score of the subjects taking medications was compared with the mean for the subjects taking no medications, and the difference was nonsignificant (main effect of group: F=0.25, df=1, 125, p=0.62).

Table 1 presents the symptom severity scores at enrollment, the end of the treatment study, and follow-up for the subjects who were contacted within 1 year of the end of the study (mean=6 months) and those contacted 1 year or more after the end of the study (mean=18 months). In multivariate analysis, the only statistically significant result was the main effect of time; contrast between time points showed that severity was less at both follow-up (F=31.5, df=1, 125, p<0.0001) and the end of the study (F=66.9, df=1, 125, p<0.0001) than at enrollment. Although the symptoms had returned to a moderate level, at follow-up they were lower than at enrollment in the treatment study (all post hoc pairwise comparisons showed statistically significant differences between time points). As can be seen in table 1, the severity scores of the two groups were very similar at all times, indicating that symptom severity did not differ between the early and later follow-up periods.

We also examined whether the subjects who improved most during treatment (i.e., had a decrease in total premenstrual daily symptom score of at least 50%) were still more improved at follow-up. When the mean follow-up severity score of the improvers (mean=2.34, SD=1.17) was compared with the mean for the remaining subjects (mean=2.23, SD=1.11), the difference was not statistically significant (F=0.38, df=1, 124, p=0.54), indicating that the greater improvement of a subset of patients during treatment was not maintained. A separate analysis of the small group that continued progesterone treatment (N=22), comparing those who had improved 50% or more during the treatment phase with the remainder in this subgroup, also showed no difference in symptom severity at follow-up.

## DISCUSSION

These data describe the course of PMS severity after 8-month treatment of women who were carefully evaluated for this disorder. The PMS symptoms tended to return after treatment, although not to their original severity levels. Although some improvement gained during treatment was maintained, overall the subjects remained moderately symptomatic.

We suggest that the original decrease in symptom levels, which occurred in both the group that received placebo and the group that received progesterone treatment, resulted as much from the treatment process and from the women's expectations of treatment as from the medication, which did not result in a statistically better outcome than did placebo. The daily symptom recording and monthly review of symptoms with clinicians, maintained by the subjects throughout the treatment study, helped the women develop a more informed understanding of their symptoms. Expert clinicians and a long-term PMS treatment program gave credibility to and validated a poorly understood condition, reducing the subjects' anxiety about their psychiatric symptoms. The patients felt that they were not alone, that someone understood their condition and cared about them—perceptions that may be essential for health. The moderate return of symptoms that followed cessation of treatment may have in part resulted from the loss of support and the absence of consistent treatment, as signified by the discontinuation of medication for PMS by most of the women contacted at follow-up.

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## New Policy Regarding Letters to the Editor

Effective immediately, Letters to the Editor critical of an article published in the *Journal* must be received within 6 weeks of the article's publication. Letters received after the deadline will not be considered and will be returned unreviewed.

# Dissociation in Women With Chronic Pelvic Pain

Edward A. Walker, M.D., Wayne J. Katon, M.D., Kathryn Neraas, M.D.,
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*Objective: The authors' goal was to determine if women with chronic pelvic pain are significantly more likely to use dissociation as a coping mechanism than women without pain. Method: The subjects were recruited from women who attended a university women's clinic during a 1-month period. Twenty-two women who reported that they had at any time in their lives experienced pelvic pain nearly every day for a period of at least 6 months were included in the study, along with 21 randomly selected women without a history of chronic pelvic pain. The 43 women were given structured sexual assault interviews and completed psychological self-report measures. Results: The women with chronic pain were significantly more likely to use dissociation as a coping mechanism, to show current psychological distress, to see themselves as medically disabled, to experience vocational and social decrements in function, and to amplify physical symptoms. They were also significantly more likely to have experienced severe childhood sexual abuse. In the total study group, women with a childhood history of sexual abuse had significantly higher scores on measures of psychological distress, somatization, and dissociation and viewed their physical health and functioning as more impaired. Conclusions: The authors discuss a model for the development of somatization, dissociation, and pain symptoms in victims of early sexual abuse.*

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Chronic pelvic pain is a frequently encountered problem in primary care. Although the exact prevalence is unknown, our recent survey of 650 women attending two ambulatory care clinics found that 38% reported pelvic pain persisting for more than 6 months at some time in their lives and 12% stated it was the chief complaint for the clinic visit (1). Studies comparing women with and without chronic pelvic pain have shown that women with pain are significantly more likely to have histories of recurrent major depression, somatization, sexual and physical abuse, and chronic psychological distress (2–4), factors that have been shown to predispose to greater use of medical care services (3, 5). Childhood sexual and physical abuse have also been shown to lead to subsequent somatization, anxiety, and depression (6, 7), and the intensity of these sequelae appears to be correlated with the duration and severity of the abuse (3).

Patients who have experienced childhood physical and sexual abuse have also been found to use dissociation as a coping mechanism more often than patients without a history of this abuse (8, 9). As defined by *DSM-III-R*, dissociation is a disturbance or alteration in the normally integrative functions of identity, memory, or consciousness.

Since chronic pelvic pain and dissociation have both been independently associated with childhood physical and sexual abuse, we hypothesized that women with chronic pelvic pain would have higher scores on measures of dissociation and would be more likely to use dissociative defenses.

## METHOD

The subjects were recruited from women attending a university women's clinic during a 1-month period. All of the women who came to the clinic during this time were given a written invitation to participate in the study by the two medically trained interviewers (K.N. and D.M). The letter stated that we were interested in speaking briefly with women who had at any time in their lives experienced pelvic pain nearly every day for a period of at least 6 months.

Twenty-two women met the inclusion criteria for medically unexplained chronic pelvic pain persisting for more than 6 months and provided informed consent. These

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**TABLE 1. Psychological Self-Report Test Scores of Women With and Without Chronic Pelvic Pain**

| Test | Women With Chronic Pain (N=22) |  | Women Without Chronic Pain (N=21) |  | Analysis |  |  |
|---|---|---|---|---|---|---|---|
|  | Mean | SD | Mean | SD | t | df | p |
| General Health Questionnaire | 11.4 | 7.4 | 3.9 | 4.7 | 3.89 | 39 | <0.001 |
| Barsky Amplification Scale | 22.0 | 6.7 | 15.6 | 7.3 | 2.93 | 39 | <0.005 |
| Dissociative Experiences Scale | 19.0 | 14.9 | 4.8 | 3.8 | 4.22 | 41 | <0.001 |
| Medical Outcomes Survey[a] |  |  |  |  |  |  |  |
| Health perception | 43.8 | 23.1 | 75.6 | 13.7 | 5.27 | 36 | <0.001 |
| Physical function | 66.5 | 27.8 | 89.2 | 16.3 | 3.14 | 36 | <0.005 |
| Role function | 57.4 | 40.3 | 89.8 | 20.0 | 3.23 | 36 | <0.01 |
| Social function | 64.7 | 30.4 | 87.6 | 18.4 | 2.87 | 36 | <0.01 |
| Mental health | 52.0 | 26.3 | 70.3 | 15.5 | 2.67 | 36 | <0.05 |

[a] Lower scores are associated with less physical, social, and role function and a worse perception of physical and mental health.

women were given a structured sexual assault interview by the two medically trained interviewers (K.N. and D.M). The interview took approximately 20 minutes and was conducted while the women waited for their appointments. The sexual assault interview was a 14-question instrument previously used in large community epidemiologic studies (10). On the basis of their responses, women were characterized as having severe childhood abuse (incest, rape, oral contact, or repeated fondling before age 14), less severe childhood abuse (exhibitionism, aborted attempts before age 14), or no abuse.

The women also completed a battery of self-report questionnaires. These included the 28-item General Health Questionnaire (11), a screening instrument that measures psychosocial distress; the short version of the Medical Outcomes Survey (12), a 17-item measure of physical and medical health perceptions and resulting physical and functional disability; the Barsky Amplification Scale (13), a 10-item rating scale for somatization; and the Dissociative Experiences Scale (14), a 28-item scale measuring the degree to which dissociation is used as a coping strategy.

Twenty-one women who came to the clinic during the same 1-month period and who did not report a history of chronic pelvic pain were randomly selected as a comparison group. They were interviewed in the same manner and completed the same psychological tests as the 22 women with chronic pelvic pain. They also provided informed consent.

Chi-square tests with Yates's correction were used to compare the two groups of women on categorical measures such as marital status, sexual abuse history, and social class, and two-tailed t tests were used to determine if the groups differed on continuous variables such as age and psychological test scores.

## RESULTS

The mean age of the 22 subjects with chronic pelvic pain was 27.6 years (SD=7.7), and their mean Hollingshead social class rating was 4.0 (SD=1.0). The mean age of the 21 patients without pain was 31.2 years (SD=7.8), and their mean Hollingshead social class rating was 3.4 (SD=1.3). The two groups did not differ significantly in age (t=1.52, df=41, n.s.) or social class rating (t=1.75, df=41, n.s.). Significantly more of the patients in the comparison group (N=17) than in the chronic pain group (N=9) were married ($\chi^2$=5.63, df=1, p<0.01).

The psychological test scores of the two groups of patients are summarized in table 1. The women with chronic pelvic pain had significantly higher dissociation scores, expressed significantly more current distress on the General Health Questionnaire, and were more likely to amplify somatic distress and perceive themselves as medically, vocationally, and socially disabled than the women who did not report pain. They were also significantly more likely to have experienced any form of childhood sexual abuse or severe childhood sexual abuse. Eighteen of the women with pain, compared with nine of the women without pain experienced any childhood abuse ($\chi^2$=5.41, df=1, p<0.02); 12 of the women with pain, compared with one of the women without pain, experienced severe childhood sexual abuse ($\chi^2$=10.37, df=1, p<0.002). The significance of the difference between women with and without pain in the number who had experienced severe childhood sexual abuse was confirmed by Fisher's exact test (p<0.0005).

Elevated dissociation scores were positively correlated with psychological distress as measured by the General Health Questionnaire (r=0.69, df=35, p<0.001) and by Medical Outcomes Survey scales relating to perception of health (r=0.70, df=35, p<0.001), impaired social functioning (r=0.56, df=35, p<0.001), and poor mental health (r=0.77, df=35, p<0.001). There were no significant correlations between high Dissociative Experiences Scale scores and physical functioning, social/occupational role functioning, or somatic amplification.

The range of Dissociative Experiences Scale scores was 1–63 in the pain group and 1–14 in the comparison group. The median score of the comparison group (4.0) was comparable to the normal median reported for adults (4.4) (14). Women with pain, however, had a median score of 17. Twenty of the women with pain, compared with only six of the comparison group, had Dissociative Experiences Scale scores above the adult norm median of 4.4. Three of the pain patients had Dissociative Experiences Scale scores above the reported

**TABLE 2. Psychological Self-Report Test Scores of Women Who Did or Did Not Experience Severe Childhood Sexual Abuse**

| Test | Women Who Experienced Abuse (N=13) | | Women Who Did Not Experience Abuse (N=30) | | Analysis | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t | df | p |
| General Health Questionnaire | 11.5 | 7.9 | 6.0 | 6.3 | 2.29 | 39 | <0.05 |
| Barsky Amplification Scale | 22.7 | 6.7 | 17.3 | 8.1 | 2.69 | 39 | <0.01 |
| Dissociative Experiences Scale | 20.7 | 15.0 | 8.4 | 10.3 | 3.12 | 41 | <0.005 |
| Medical Outcomes Survey[a] | | | | | | | |
| Health perception | 37.1 | 25.3 | 70.0 | 17.3 | 4.55 | 36 | <0.001 |
| Physical function | 64.8 | 25.0 | 84.1 | 22.9 | 2.24 | 36 | <0.05 |
| Role function | 60.0 | 37.6 | 80.7 | 32.2 | 1.67 | 36 | n.s. |
| Social function | 70.0 | 27.0 | 80.0 | 26.7 | 1.01 | 36 | n.s. |
| Mental health | 43.2 | 24.1 | 68.9 | 17.8 | 3.51 | 36 | <0.001 |

[a] Lower scores are associated with less physical, social, and role function and a worse perception of physical and mental health.

median for psychiatric inpatients with posttraumatic stress disorder (PTSD) (31.3), and one had a score above the median for patients with multiple personality disorder (57.1).

We divided the entire study group of 43 women into those with (N=13) and those without (N=30) childhood histories of severe sexual abuse and compared the psychological test scores of these two groups (table 2). Women with a childhood history of severe sexual abuse had significantly higher scores on measures of psychological distress, somatization, and dissociation and viewed their physical health and functioning as more impaired.

## DISCUSSION

As demonstrated in previous studies (2–4), the women in this study who reported chronic pelvic pain had significantly more psychological distress and were more likely to amplify physical sensations than did the women who did not report such pain. The women who experienced pelvic pain perceived their health and social and vocational functioning as more impaired and were significantly more likely to have experienced severe childhood sexual abuse. As hypothesized, women with chronic pelvic pain were also significantly more likely to report more dissociative experiences than the comparison group.

Dissociative defenses may develop to help a person adapt to overwhelming painful experiences such as abuse or trauma. Dissociative mechanisms may alter perceptions (derealization, depersonalization) and allow the person to forget (psychogenic amnesia) or even completely disown the experience as occurring in another person (multiple personality) (8). However, the dissociated and repressed painful memories are not completely hidden or dormant and tend to return as nightmares, flashbacks, and floods of feelings and sensations related to the original experiences (8, 9). These sensations and feelings often can occur as vivid full memories and emotions or perhaps, more commonly, as bits and pieces of the original experience. Intense autonomic arousal may occur when a stimulus elicits a memory of abuse without an accompanying full visual or cognitive schema, or both can be experienced simultaneously (9). Social and emotional withdrawal in victims of PTSD have been hypothesized as coping mechanisms that enable the patient to avoid stimuli that evoke aversive visual and autonomic memories of trauma.

The high dissociation scores in this group of women with self-reported medically unexplained chronic pelvic pain may be the somatic representation of the severe physical and/or emotional traumatization that occurs secondary to childhood sexual and, possibly, physical abuse. Thus, the patient with chronic pelvic pain may experience the pain as a partial "memory" of the abuse without being consciously aware of the full extent of the memory (i.e., the physical, autonomic, and emotional traumatic memory of the abuse) (9). The symptom of pelvic pain is also often associated with dyspareunia and sexual avoidance (2). This may be an adaptive response that allows the patient to avoid stimulating more complete memories of painful childhood sexual victimization.

Although a dissociative coping style might be an adaptive response to early trauma, it can interfere with the proper diagnosis and treatment of women with disorders such as chronic pelvic pain. Women who have experienced early physical or sexual abuse sometimes repress it, deny it, or withhold this information from an interviewer due to fear of social consequences, thus limiting the accuracy of a diagnostic interview. Our findings suggest that the measurement of dissociation may provide a useful, indirect assessment of the possibility of previous sexual abuse in women with chronic pelvic pain.

Dissociation may also influence the patient's response to treatment. Chu and Dill (8) recently found that psychiatric inpatients with histories of childhood physical and sexual abuse had a higher level of dissociative symptoms and had experienced significantly more hospitalizations and more somatic treatments (medications and ECT) than those without such histories. These patients were usually not diagnosed as having dissociative symptoms; the treatment data suggest that this lack of accurate diagnosis may be associated with repeated hospitalizations and resistance to treatment. Although the Dissociative Experiences Scale scores in our study group were not as high as those reported in a psychiatric inpatient setting, they were surprisingly high for a group of ambulatory medical patients.

Our recent pilot study of antidepressant treatment in women with chronic pelvic pain (15) suggested that patients with histories of significant childhood sexual abuse were more likely to drop out of the study due to excessive medication side effects and to show poor response to pharmacological therapy alone than were patients without abuse histories. Women with chronic pelvic pain who have also experienced childhood sexual abuse may require multimodal treatment strategies, including behavioral and insight-oriented psychotherapies, in addition to pharmacotherapy (15).

The findings reported in this paper should be considered preliminary because of the small number of subjects, possible bias in subject selection, and the limitations noted in obtaining a valid sexual abuse history. We also used a random comparison sample rather than a matched comparison group and did not record the patients' medical diagnoses. Nevertheless, the results of this study suggest that it is important to continue to study women with chronic pelvic pain to ascertain rates of PTSD, severe dissociative disorders, and multiple personality disorder because high scores on the Dissociative Experiences Scale are not diagnostic but are associated with these disorders. A larger study group would also allow multivariate analysis to determine the factors most highly correlated with dissociative symptoms (i.e., psychological distress, severe childhood physical and/or sexual abuse, and somatization).

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# Effect of Sleep Deprivation on Brain Metabolism of Depressed Patients

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*Objective:* *Sleep deprivation is a rapid, nonpharmacologic antidepressant intervention that is effective for a subset of depressed patients. The objective of this study was to identify which brain structures' activity differentiates responders from nonresponders and to study how metabolism in these brain regions changes with mood.* *Method:* *Regional cerebral glucose metabolism was assessed by positron emission tomography (PET) with [$^{18}$F]deoxyglucose (FDG) before and after total sleep deprivation in 15 unmedicated awake patients with unipolar major depression and 15 normal control subjects, who did the continuous performance test during FDG uptake.* *Results:* *After sleep deprivation, four patients showed a 40% or more improvement on the Hamilton Rating Scale for Depression. Before sleep deprivation the depressed responders had a significantly higher cingulate cortex metabolic rate than the depressed nonresponders, and this normalized after sleep deprivation. The normal control subjects and nonresponding depressed patients showed no change in cingulate metabolic rate after sleep deprivation.* *Conclusions:* *Overactivation of the limbic system as assessed by PET scans may characterize a subset of depressed patients. Normalization of activity with sleep deprivation is associated with a decrease in depression.*

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Sleep deprivation has been shown to have a rapid, nonpharmacologic antidepressant effect in studies involving over 1,500 patients (1–3). In normal subjects sleep deprivation is associated with diminished vigilance and decreased metabolism in the thalamus and midbrain, according to studies using positron emission tomography (PET) (4). Since normal and depressed subjects seem to have different responses to sleep deprivation (1), a different regional metabolic response to sleep deprivation might well occur in such patients, perhaps involving the cingulate and other limbic structures. The limbic system has been hypothesized to be involved in mood (5). In this report we present the results of what we believe to be the first study of sleep deprivation in depression using PET with [$^{18}$F]deoxyglucose (FDG) to assess limbic system metabolic correlates of mood and the antidepressant effects of sleep deprivation.

## METHOD

### *Subjects*

The subjects in this study were 15 normal control subjects (nine women, six men; mean age=31.9 years, SD=9.1) and 15 depressed outpatients (12 women, three men; mean age=30.5 years, SD=10.2). They were studied with FDG PET scans after a night of normal sleep and again after all-night sleep deprivation. All depressed subjects met the *DSM-III-R* criteria for unipolar major depression and had scores on the Hamilton Rating Scale for Depression of 17 or greater at the time of screening. Neither the patients nor the normal subjects had taken psychoactive medications for at least 2 weeks before the study. Ten of the patients had never taken antidepressants. The other five had previously received amitriptyline, desipramine, or alprazolam. The

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mean time without medication for these five patients was 4.7 months (SD=4.0). They reported that they had achieved clinical response to these medications and had relapsed when the medications were discontinued.

All subjects were free of physical disorders. The control subjects and their first-degree relatives were determined to be without mental disorders. Eight of the 15 normal control subjects in this study were reported on in our previous study of normal subjects (4). The depressed and normal control subjects were recruited through newspaper advertisements. Informed consent was obtained after the procedure was fully explained.

### *Experimental Protocol and Clinical Assessment*

The subjects were deprived of sleep and kept under continuous supervision from approximately 7:00 a.m. until after the scanning procedure the following afternoon at 1:00–5:00 p.m. Mood was measured with the 21-item Hamilton questionnaire, from which questions 4–6 were deleted because they deal with how the subject sleeps and are not applicable when the subject is deliberately deprived of sleep. The questionnaire was administered between 9:00 a.m. and noon on the baseline PET scan day (after a night of normal sleep) and on the second PET scan day (after sleep deprivation). On the basis of our previous findings (6), patients were defined as responders to sleep deprivation if their Hamilton depression scores decreased by at least 40% after total sleep deprivation. The FDG PET procedure has been described previously (7). During the uptake of FDG the subjects did the continuous performance test, a visual vigilance task (8).

### *Brain Imaging Protocol*

Approximately 45 minutes after the injection of FDG, nine slice images were obtained. The repositioning of the patients during the two studies was accurate to within 2 mm because for each patient we reused a custom-molded thermoplastic mask that was aligned with the anatomical landmarks of the lateral canthus and external auditory meatus. The scan was transformed to a glucose metabolic rate as described previously (7).

Cortical metabolic rates were measured by using our cortical peel technique (4). Subcortical structures were assessed by using stereotaxic coordinates derived from a standard neuroanatomical atlas (9), as we have previously described (7). We analyzed the absolute metabolic rate, which was expressed in micromoles of glucose per 100 g of tissue per minute.

The brain was divided into eight main systems: lateral cortex (average of frontal, temporal, parietal, and occipital lobes), medial cortex (precuneus, paracentral, medial frontal, rectal gyri, calcarine, and medial temporal), limbic system (average of amygdala, hippocampus, and cingulate), basal ganglia (average of caudate, putamen, and globus pallidus), thalamus, white matter (average of frontal white matter, corpus callosum, and optic radiation), midbrain, and cerebellum.

Statistical analysis comprised a four-way repeated measures multivariate analysis of variance (MANOVA) with BMDP 4V software (10), followed by post hoc t tests. The dimensions of the MANOVA were diagnostic group, brain system, hemisphere, and sleep condition. All significant interactions between group and sleep condition are reported. When significant interactions between brain regions and conditions were observed, we used simple effects analysis and t tests as post hoc contrasts.

## RESULTS

### *Clinical Response*

Of the 15 depressed patients, four were identified as responders (decrease in Hamilton depression score ≥40%). The responders and nonresponders did not differ significantly in mean age (responders: mean=29.8 years, SD=10.3; nonresponders: mean=30.8 years, SD=10.6), sex distribution (responders: four women; nonresponders: eight women and three men), or mean baseline Hamilton depression score (responders: mean=19.8, SD=5.9; nonresponders: mean=21.3, SD=7.3). The responders showed a significantly greater decrease in depression score; their mean Hamilton score after sleep deprivation was 6.0 (SD=2.1), compared to 19.9 (SD=9.4) for the nonresponders.

### *Changes in Regional Metabolic Rates*

At baseline the responders differed significantly from the nonresponders in their metabolic rate pattern (see table 1). Simple effects analysis and follow-up t tests revealed that the baseline glucose metabolic rate in the limbic system was significantly higher in the depressed responders than in either the depressed nonresponders or the normal control subjects (see table 1). Similar analyses indicated that the depressed responders had a significantly higher metabolic rate in the medial cortex than did the normal control subjects. No differences in whole brain metabolic rate were found, i.e., the main effect of subject group was not significant.

There was a significant difference in the patterns of change in absolute brain system metabolic rates after sleep deprivation among the responders, nonresponders, and normal control subjects (see table 1). The responders experienced a significant decrease in their initially high metabolic rate in the limbic system after sleep deprivation, whereas neither the normal control subjects nor the nonresponders showed a significant change as indicated by ANOVA. Again, no main effect across all structures was confirmed, indicating regional specificity for the effect.

The rates in the cingulate, amygdala, and hippocampus were measured to obtain the limbic system average (see figures 1 and 2). At baseline the depressed responders had significantly higher cingulate and amygdala glucose metabolic rates than either the nonresponders or

**TABLE 1. Brain Metabolism and Visual Vigilance Before and After Sleep Deprivation in Depressed Responders, Depressed Nonresponders, and Normal Subjects[a]**

| Variable and Condition (before or after sleep deprivation) | Responders (N=4) | | Nonresponders (N=11) | | Normal Subjects (N=15) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Glucose metabolic rate (μmol/100 g tissue/min) | | | | | | |
| Cortical surface | | | | | | |
| Before | 31.5 | 6.3 | 26.2 | 6.5 | 24.0 | 6.6 |
| After | 27.4 | 6.9 | 26.0 | 9.9 | 23.7 | 7.1 |
| Medial cortex | | | | | | |
| Before | 38.3[b] | 7.4 | 31.1 | 7.4 | 28.3 | 7.4 |
| After | 33.2 | 8.3 | 31.2 | 11.0 | 28.3 | 8.0 |
| Limbic system | | | | | | |
| Before | 26.6[c] | 8.3 | 19.8 | 3.5 | 18.9 | 4.6 |
| After | 21.5 | 6.4 | 19.1 | 7.1 | 18.5 | 5.7 |
| Thalamus | | | | | | |
| Before | 31.0[d] | 5.1 | 25.1[e] | 6.0 | 26.6 | 6.8 |
| After | 28.1 | 9.3 | 26.1 | 10.7 | 23.6 | 7.9 |
| Basal ganglia | | | | | | |
| Before | 34.4 | 6.4 | 27.7 | 6.7 | 27.1 | 6.5 |
| After | 27.6 | 6.5 | 27.0 | 11.0 | 25.7 | 8.7 |
| White matter | | | | | | |
| Before | 21.1 | 5.6 | 17.5 | 4.6 | 16.2 | 4.3 |
| After | 20.1 | 5.4 | 18.1 | 6.3 | 17.9 | 5.3 |
| Midbrain | | | | | | |
| Before | 21.9 | 8.9 | 17.1 | 4.1 | 17.1 | 4.4 |
| After | 17.6 | 5.9 | 16.5 | 7.6 | 15.6 | 4.7 |
| Cerebellum | | | | | | |
| Before | 22.0[f] | 8.4 | 18.9 | 4.5 | 19.2 | 5.4 |
| After | 18.0 | 7.2 | 20.4 | 11.0 | 16.6 | 5.6 |
| Score on continuous performance task (d′) | | | | | | |
| Before | 4.1[g] | 0.0 | 3.4 | 0.8 | 3.3 | 1.0 |
| After | 3.5[h] | 0.5 | 2.9[i] | 0.9 | 2.8[j] | 0.9 |

[a] Significant Condition by Brain System by Group interaction (F=2.41, df=14, 40, p=0.02) and System by Group interaction for baseline only (F=2.60, df=14, 40, p=0.009) (MANOVA).

[b] Significantly higher in responders than in normal subjects (t=2.41, df=17, p=0.03).

[c] Significantly higher in responders than in nonresponders (t=2.25, df=12, p=0.04) or normal subjects (t=2.54, df=17, p=0.02) (F=4.13, df=2, 26, p=0.02; Bonferroni criterion: n.s.). Negative correlation with change in visual vigilance (r=–0.95, df=2, p<0.05).

[d] Negative correlation with change in visual vigilance (r=–0.96, df=2, p<0.05).

[e] Positive correlation with change in visual vigilance (r=0.71, df=9, p<0.05).

[f] Negative correlation with change in visual vigilance (r=–0.97, df=2, p<0.05).

[g] Significantly higher in responders than in nonresponders (t=2.68, df=12, p<0.05) or normal subjects (t=3.19, df=17, p<0.05).

[h] Significantly lower than at baseline (t=2.32, df=3, p<0.05).

[i] Significantly lower than at baseline (t=3.58, df=9, p<0.05).

[j] Significantly lower than at baseline (t=4.01, df=14, p<0.05).

the normal control subjects. In contrast, the glucose metabolic rates in the hippocampus did not significantly differ between the responders and either the nonresponders or the normal control subjects. The glucose metabolic rate in the cingulate decreased significantly after sleep deprivation for the responders, whereas the nonresponders and normal control subjects showed little change. The amygdala did not show a statistically significant decrease in the responders. These findings were confirmed by a three-way ANOVA interaction (Diagnostic Group by Brain System by Sleep Condition: F=2.74, df=3.69, 48.02, p<0.05, Greenhouse-Geisser corrected) and exploratory post hoc t tests.

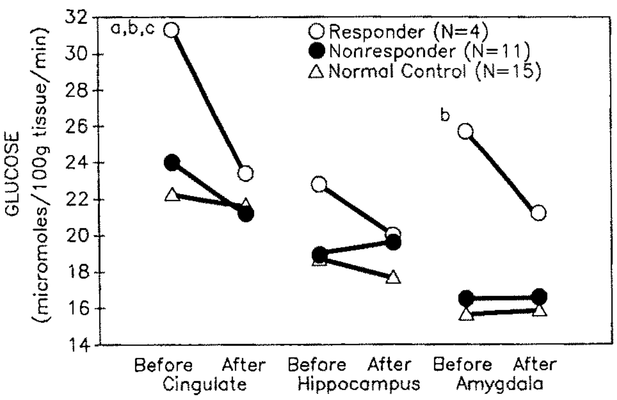
After sleep deprivation all of the responders showed a decrease in the cingulate of at least 2.0 μmol glucose/100 g tissue per minute. Of the 11 nonresponders, four showed similar decreases, two showed increases, and five showed no change.

Vigilance was assessed quantitatively by using the d′ measure (4). Greater vigilance is associated with a higher d′ value. Before sleep deprivation the mean d′ vigilance score on the continuous performance test was higher for the depressed responders than for either the depressed nonresponders or the normal control subjects (see table 1). All three groups had lower d′ values after sleep deprivation, and the change was significant for all three groups according to paired t tests, but the differences did not vary between groups.

Significant negative correlations between change in vigilance score and baseline metabolic values in the limbic system, thalamus, and cerebellum were found for the depressed responders (see table 1). A significant positive correlation was found between the baseline thalamus metabolic value and change in d′ score for the depressed nonresponders.

Hypofrontality values were calculated by taking the

**FIGURE 1. Mean Glucose Metabolic Rates for Limbic System Structures Before and After Sleep Deprivation in Depressed Responders, Depressed Nonresponders, and Normal Subjects**

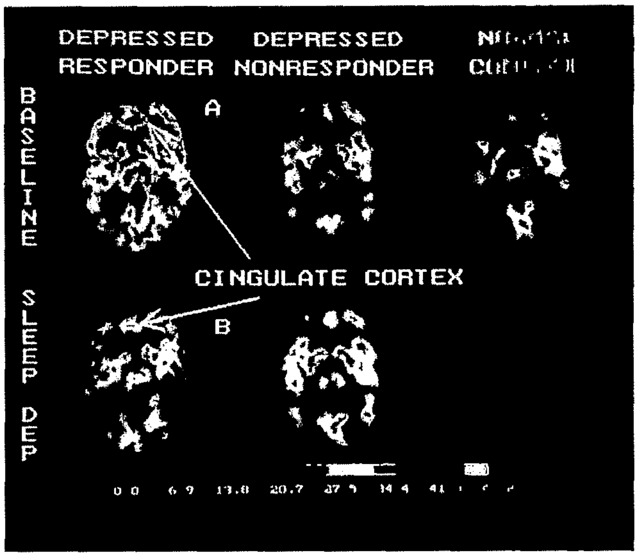


[a] Significant difference between responders and nonresponders at baseline (t=2.69, df=12, p=0.02).

[b] Significant difference between responders and normal subjects at baseline for cingulate (t=2.75, df=17, p=0.01) and for amygdala (t=3.09, df=17, p=0.01)..

[c] Significant difference between rates before and after sleep deprivation (t=2.42, df=17, p=0.03).

**FIGURE 2. PET Scans for Depressed Responders, Depressed Nonresponders, and Normal Subjects Before and After Sleep Deprivation[a]**



[a] All images are displayed with the same metabolic rate scale, shown as a bar at the bottom. Note the high cingulate activity (A) in the responders before sleep deprivation and the normalization of cingulate activity (B) after sleep deprivation.

metabolic rates for the four frontal lobe segments in each hemisphere (superior, middle, inferior frontal gyri, and precentral gyrus) and dividing these by the occipital lobe metabolic rate. No significant group differences were found between the depressed responders and either the depressed nonresponders or normal control subjects according to ANOVAs or t tests.

## DISCUSSION

The baseline metabolic rates for the cingulate cortex and amygdala were significantly higher in the depressed patients who responded to sleep deprivation than in the patients who did not respond or the normal control subjects. The metabolic rate for the cingulate fell significantly toward normal in the depressed responders after sleep deprivation, while that for the amygdala decreased nonsignificantly. These findings should be viewed as preliminary because of the relatively small number of responders and should be replicated in a larger cohort of depressed patients.

On the basis of our findings, we tentatively hypothesize that overactivation in the limbic system as measured by FDG PET scans is present in a subset of depressed patients before sleep deprivation. We suggest that in this subset sleep deprivation reduces depression by reducing the overactivity in these regions. These interpretations are consistent with earlier suggestions (11, 12) that some depressed patients are "overaroused" and that sleep deprivation acts by reversing this abnormality.

A subset of depressed patients have subnormal slow wave sleep (13, 14), and it may be this subset who respond best to sleep deprivation (15). Slow wave sleep has been hypothesized (16, 17) to slow down metabolic activity as a way of dissipating the heat load incurred during awake time. An impaired ability to activate slow wave sleep in a subset of depressed patients could result in an inability to slow down metabolism. Depressed patients have been shown to have abnormally high core body temperatures during the sleep period (18–20), and this finding is especially true in the subtype of patients who respond to sleep deprivation (21). Wehr (22) has hypothesized that prolonged awake time might reduce body metabolism. Prolonged awake time (i.e., sleep deprivation) might act like slow wave sleep to reduce body metabolism, whereas REM sleep may maintain high body temperature.

In addition to subnormal slow wave sleep and higher than normal nocturnal temperature, high levels of thyroid hormones differentiate the subset of depressed patients who respond to sleep deprivation (23). Higher than normal levels of thyroid hormones may be a neuroendocrine correlate of overarousal in this subset of depression.

We also observed higher baseline vigilance scores (as measured by the d′ on the continuous performance test) in the depressed responders than in either the nonresponders or the normal control subjects. This observation is consistent with the theory of overarousal in depression, since vigilance is associated with arousal (11, 12). In a study of sleep deprivation in 16 depressed patients by Bouhuys et al. (24), self-reported arousal was correlated with mood response. The cingulate cortex has been implicated in maintenance of vigilance (25), which is also associated with arousal (26).

In a previous study (7), the cingulate gyrus was the only cortical structure with a significantly higher glucose metabolic rate during REM sleep than during the normal waking state. REM sleep is associated with an increase in cholinergic activity and a decrease in aminergic activity (27). Short REM latency in depressed patients may also be an indicator of hyperarousal. Further studies are needed to determine the causal chain of events.

The cingulate cortex is innervated by cholinergic input from cells in the basal forebrain (28, 29). Depressed patients have been hypothesized to have an overactive cholinergic system (30), in part because of a supersensitive responsiveness to the cholinergic REM induction test (31, 32). An overactive cingulate cortex might also be associated with an underactive aminergic system, which has also been hypothesized for depression (30). Depressed patients treated with sertraline, a serotonergic reuptake inhibitor, were found to have significantly decreased cingulate cortex metabolism, as assessed by PET scans (J.C. Wu, unpublished data). Enhancement of serotonergic function by lithium has been shown to prevent relapse with recovered sleep after total sleep deprivation (33) or after partial sleep deprivation (34). Decreasing serotonergic function through tryptophan depletion has been found to precipitate a depressogenic relapse in patients who have responded to antidepressants (35).

The large decrease seen in the cingulate cortex of the depressed responders after sleep deprivation was seen in only a few of the nonresponders and normal control subjects. In our previous study of normal subjects (4), in which eight of the 15 normal control subjects in this study were also studied, the limbic system did not show a significant decrease in glucose metabolic rate after sleep deprivation. Our present analysis with the larger cohort of normal control subjects also shows no significant decrease in the cingulate cortex rate for normal subjects. The limbic system was the only one of eight brain systems (including the dorsolateral cortex, medial cortex, basal ganglia, thalamus, midbrain, white matter, cerebellum) that showed a significant difference between depressed responders and both the normal subjects and depressed nonresponders.

The method used to study the regions of interest relies on stereotaxic coordinates based on a neuroanatomical atlas (9). Using the Talairach atlas (36), we estimated the volume of the hippocampus to be 3000 mm$^2$. The approximate dimensions of the hippocampus are 12 mm thick by 25 mm long by 10 mm wide. The dimensions of the hippocampus can easily accommodate our stereotaxic boxes, which are 10 mm thick by 6 mm long by 6 mm wide. The approximate dimensions of the amygdala are 8 mm thick by 12 mm long by 10 mm wide, for a total volume of approximately 960 mm$^2$. Although it is smaller, this structure can also accommodate our 10 mm by 6 mm by 6 mm stereotaxic box. Talairach et al. (36) and Vanier et al. (37) have demonstrated that a proportional system for localizing structures in the brain is much more reliable than using distances from bony landmarks in millimeters. This is because a proportional-based system normalizes the brains of different individuals and permits individual cases to be reduced to a common scale. Random variation caused by individual differences in brain proportions, vertical position of the plane studied, and variation in head position and reposition would all tend to create random error and diminish group differences.

The higher right precentral gyrus metabolic rate in the depressed responders than in the depressed nonresponders is consistent with the hyperfrontality in depressed unipolar patients previously reported by our group (38), but it is not consistent with the hypofrontality reported by Baxter et al. (39). This may be due to the differences in the cognitive task studied during the glucose-uptake period.

This study has some important clinical implications. It may be possible to better characterize subtypes of depression with different responses to treatment by using an objective biological measure (e.g., PET scans) as a basis for classification. This study provides evidence for a distinct subtype of depression with overactive limbic system metabolism that responds to sleep deprivation.

## ADDENDUM

Since this manuscript was submitted, similar findings were presented by D. Ebert, H. Feistel, and A. Barocka at the 5th World Congress of the World Federation of Societies of Biological Psychiatry, Florence, Italy, June 9–14, 1991. Using technetium $^{99m}$Tc HMPAO SPECT, they showed that responders to sleep deprivation, but not nonresponders, were more hyperperfused in the limbic system than normal control subjects.

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# Undetected HIV Infection Among Acutely Ill Psychiatric Inpatients

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*Serological testing of waste bloods revealed that 25 (7%) of 350 acutely ill psychiatric inpatients had HIV infection. Eight of the 10 HIV-positive patients whose serological status was not recorded on admission were discharged with their status still unrecorded and presumably undetected. Thirty-nine (51%) of the 77 inpatients with HIV-related risk behaviors identified on admission were discharged with no record of their having been serologically tested before or during hospitalization.*

(Am J Psychiatry 1992; 149:544–545)

With the established efficacy of early medical interventions for patients with HIV infection (1), serological testing has been encouraged for those at risk (2); however, current estimates are that most at-risk individuals have not yet been tested (3). HIV testing may be especially important for at-risk individuals admitted to a psychiatric hospital because their mental changes may be caused or worsened by the direct effects of HIV on the brain (4). Further, we have found high rates of HIV risk behaviors (18%–22%) among acutely ill psychiatric inpatients (5, 6).

Despite the medical and diagnostic indications for voluntary HIV testing, psychiatric inpatients may be too disturbed or distrustful either to reveal risk factors or to provide informed consent for HIV testing. Understandable concerns about disclosure in the medical record and to third-party payers may be an additional reason for refusal, and HIV testing may be inadvisable during an acute psychiatric illness. Because of these inherent problems, many HIV-positive psychiatric inpatients may go undetected during hospitalization.

To examine this possibility, we determined the actual number of HIV-positive inpatients in our facility and then reviewed medical records to examine how many HIV-positive inpatients were discharged with their serological status unrecorded and presumably undetected.

## METHOD

After institutional review board approval, a seroprevalence study was conducted on all psychiatric inpatients between 18 and 55 years old who were admitted to an acute inpatient facility in Manhattan from November 1989 through May 1990. The waste residue of each patient's admission blood chemistry work was serologically tested for HIV. We reviewed each patient's admission history to estimate known HIV-related risk behaviors such as males having sex with males and parenteral drug use as well as factors of lower risk, such as having five or more heterosexual partners in 1 year and/or being the heterosexual partner of a person known or suspected to be HIV positive. Also recorded were the patient's sex, age, race, social class, ethnicity, and whether his or her HIV status was positive, negative, or unknown. This chart information was connected to the waste blood and assigned a random number. All other data were destroyed, including the patient's name and chart number. This "unlinking" helped protect patients' anonymity. The charts,

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including laboratory results and discharge summaries, of all patients admitted during the study period, were reviewed by a research assistant 6 months later to determine whether the patient was known to be HIV positive or HIV negative at discharge. The reviewer was blind to data from both the admission chart review and the seroprevalence survey.

## RESULTS

Of the 383 patients admitted during the study period, sufficient waste bloods were available for 350 (91%). Twenty-five (7%) of these patients were HIV positive. Ten of the 25 patients were not recorded as being HIV positive on admission. Two of these 10 patients were serologically tested during hospitalization. Thus, the great majority of HIV-positive inpatients whose serological status was unrecorded on admission left the hospital with their seropositivity still unrecorded.

An attempt was made to identify variables associated with detection. As shown in table 1, on admission only three of the 25 patients who were HIV positive had no recorded risk factors according to their charts, and recorded seropositivity was positively associated with males having sex with males. No relationship was found between recorded seropositivity at admission and gender, race, age, ethnicity, or social class; however, because of the small number of HIV-positive patients, the risk of an erroneous negative finding (type II error) is high.

We examined how many inpatients with HIV-related risk factors were serologically tested before or during hospitalization. On admission, risk factors were recorded for 77 (22%) of the 350 inpatients (32 males having sex with males, 32 parenteral drug use, and 13 other). Reports of previous testing indicated that 15 of these 77 patients were HIV positive and that three were HIV negative. Of the remaining 59 patients with recorded risk factors, the HIV antibody status of 20 was determined during hospitalization (two were HIV positive, and 18 were HIV negative). Thus, of 77 inpatients with recorded risk factors, 39 (51%) left the hospital with their serological status still unrecorded (five who were HIV positive and 34 who were HIV negative).

## DISCUSSION

Three major findings emerged from this study. First, psychiatric hospitalization was not associated with detection of HIV positivity. Of the 10 HIV-positive inpatients whose serological status was not known on admission, eight were not serologically tested during hospitalization and were discharged with their HIV infection still unrecorded and presumably undetected.

Second and related to the first finding, serological testing was not vigorously pursued during hospitalization. Among the 59 previously untested inpatients with HIV-related risk factors identified on admission, the HIV antibody status of only 20 (34%) was determined during their hospital stay.

**TABLE 1. HIV-Related Risk Factors Among HIV-Positive Inpatients Whose Serological Status Was or Was Not Recorded**

| Risk Factor | Patients With Recorded HIV Infection (N=15) | Patients With Unrecorded HIV Infection (N=10) |
|---|---|---|
| Males having sex with males[a] | 10 | 2 |
| Parenteral drug use | 3 | 2 |
| Males having sex with males and parenteral drug use | 1 | 0 |
| Other | 1 | 3 |
| None documented | 0 | 3 |

[a] $\chi^2=4.86$, df=1, $p<0.05$.

Third and more encouraging, severe mental illness did not generally preclude determining risk factors and HIV infection. Among the 25 HIV-positive patients, a history of risk factors was recorded on admission for 22, and 15 knew that they were HIV positive.

The study was limited to a single hospital in an area of the Northeast where the prevalence of HIV seropositivity is high and may not reflect the experience in other hospitals, particularly those in a low seroprevalence area. It could be argued that both physicians and subjects in a high seroprevalence area are more sensitive to the need for HIV testing than their counterparts in hospitals in lower seroprevalence areas. It could equally be argued that this awareness, together with concerns for confidentiality, greater experience, and availability of other test sites, might result in a decision not to test for HIV in the hospital setting.

Given the medical and diagnostic indications for determining HIV serological status in at-risk psychiatric inpatients, these findings suggest that further studies be conducted to identify factors impeding HIV testing of this population.

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# Agitation and Postdexamethasone Cortisol Levels in Alzheimer's Disease

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*The clinical correlates of hypothalamic-pituitary-adrenal (HPA) functioning were examined in 29 patients with probable Alzheimer's disease. The 8:00 a.m. postdexamethasone cortisol levels of these patients were highly correlated with higher agitation scores but not with the degree of depressed mood or memory impairment. The possible neural basis for the association between hypercortisolism and behavioral disturbance in Alzheimer's disease warrants further exploration and replication.*

(Am J Psychiatry 1992; 149:546–548)

Up to 50% of patients with Alzheimer's disease demonstrate nonsuppression of cortisol following dexamethasone administration (1–5), and mild elevations of basal cortisol have also been described (4, 6). However, the clinical significance and underlying pathogenetic mechanism of hypercortisolism in Alzheimer's disease are poorly understood. Greater hypothalamic-pituitary-adrenal (HPA) axis activity may reflect changes in cortical or subcortical function intrinsic to the Alzheimer's disease process, may be a nonspecific result of neuronal degeneration, or could be the end result of behavioral complications associated with the disease process.

This study explored the relationship between indexes of HPA axis function (basal cortisol and postdexamethasone cortisol levels) and specific aspects of behavior and cognition in 29 carefully characterized patients with Alzheimer's disease.

## METHOD

### *Subjects*

Twenty-nine patients with a mean age of 67.24 years (SD=7.53) (20 men and nine women) who met the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for probable Alzheimer's disease (7) participated in this study. All subjects were inpatients, were physically healthy, and were free of medications that could affect HPA axis functioning for at least 3 weeks before testing. Informed consent was obtained from all patients and/or their next of kin.

### *Rating Scales*

Cognitive and noncognitive function in the patients with Alzheimer's disease was evaluated by using the 21-item version of the Alzheimer's Disease Assessment Scale (8, 9). Agitation was defined as the sum of the items "uncooperative," "pacing," "increased motor activity," and "tremors" on this scale. Depression was defined as the sum of the items "tearful" and "depressed mood." Psychosis was defined as the sum of the items "hallucinations" and "delusions." These items are all scored from 0 (not present) to 5 (very severe). The memory impairment score was the sum of errors on items "word recall" (scored 0–10) and "word recognition" (scored 0–12); a higher score indicates more severe impairment. The severity of dementia in the 29 patients was assessed by using the Blessed Dementia Scale (10), a 33-point scale on which higher scores indicate greater impairment, and the Memory and Information Test (10), a 20-point scale on which lower scores indicate greater impairment. The mean score of the 29 patients on the Blessed Dementia Scale was 20.07 (SD=7.91); their mean score on the Memory and Information Test was 5.83 (SD=5.00).

### *Procedure*

Blood for determining basal cortisol levels was drawn from all patients at 12:00 noon, 4:00 p.m., 8:00 p.m., and 11:00 p.m., and the mean of these four samples was

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**TABLE 1. Pairwise and Multiple Correlations of Alzheimer's Disease Assessment Scale Variables and Indexes of HPA Axis Function in 25 Patients With Alzheimer's Disease**

| | Pairwise Correlation (r) | | | | | |
|---|---|---|---|---|---|---|
| | | Mean Postdexamethasone Cortisol | | | | |
| Measure From Alzheimer's Disease Assessment Scale | Mean Basal Cortisol | 8:00 a.m. | 12:00 noon | 4:00 p.m. | 11:00 p.m. | Multiple Correlation (R) |
| Agitation | –0.00 | 0.65[a] | 0.42[b] | 0.28 | 0.54[a] | 0.69[c] |
| Memory impairment | 0.30 | 0.04 | 0.23 | 0.34 | 0.13 | 0.47 |
| Depression | 0.01 | –0.05 | 0.21 | 0.06 | –0.06 | 0.41 |

[a] $p<0.01$.
[b] $p<0.05$.
[c] $p=0.02$.

calculated as the basal cortisol level. The dexamethasone suppression test (DST) was performed in the standard manner. Cortisol levels were determined at 8:00 a.m., 12:00 noon, 4:00 p.m., and 11:00 p.m. following the administration of 1 mg of oral dexamethasone at 11:00 p.m. the night before. Samples were centrifuged within 15 minutes and were stored at –20 °C until assayed. Plasma cortisol was assayed by using a radioimmunoassay with kits obtained from ICN/Micromedic Pharmaceuticals of Carson, Calif. The intra-assay and interassay coefficients of variation were 6% and 10%, respectively.

### *Data Analysis*

The data were analyzed by using multiple regression analyses. Agitation, depression, and memory impairment scores on the Alzheimer's Disease Assessment Scale were the dependent variables, and mean basal cortisol and four postdexamethasone cortisol levels were the independent variables. Because baseline cortisol levels were not available for four of the patients, the overall analysis included 25 patients. Multiple regression analyses were also used to determine whether there was a significant association of any of the dependent variables with age, gender, relative weight, duration of illness, and age at onset. For this part of the analysis, data were available for 27 patients.

## RESULTS

Table 1 presents pairwise correlations of the five independent variables with the three dependent variables as well as the multiple correlation coefficients. For the dependent variable agitation, the overall multiple correlation was significant (F=3.45, df=5, 19, p=0.02). Of the five predictors, the largest beta (1.13) (t=2.5, p=0.02) was for the 8:00 a.m. postdexamethasone cortisol level. For the other dependent variables (memory impairment and depression), neither of the multiple correlations was significant (p>0.10 in both cases).

None of the multiple correlations of the dependent variables with the covariates—age at onset, illness duration, gender, relative weight, and age—was significant (p>0.10 for all analyses).

## DISCUSSION

The major finding in this study is that postdexamethasone cortisol levels are associated with greater agitation in patients with Alzheimer's disease. The relationship between hypercortisolism and agitation is similar to the reported findings in depressed patients, where nonsuppression on the DST is also associated with agitation (11, 12). A previous study from our center (4) found a correlation between the 8:00 a.m. postdexamethasone cortisol level and the number of major but not minor symptoms of depression. In that study, major symptoms were those usually associated with endogenous depression, including agitation, psychomotor retardation, and loss of interest, symptoms that are reflected in behaviors similar to those identified by the agitation score on the Alzheimer's Disease Assessment Scale. Thus, it appears that postdexamethasone hypercortisolism may be associated with agitated behavior rather than with depressed mood per se.

If HPA axis abnormalities in Alzheimer's disease are consistently associated with a particular behavioral complication such as agitation, these indexes may be a useful marker to monitor response to pharmacological or other therapeutic interventions in this population. However, all reports of associations or lack thereof between symptoms and HPA axis measures must be interpreted in the light of the range of behavior in the patients studied. Until now, almost all studies exploring HPA axis function in Alzheimer's disease have used only patients without substantial behavioral disturbance. A relationship between postdexamethasone cortisol level and agitation in our relatively nonbehaviorally disturbed group of patients with Alzheimer's disease suggests that future studies need to explore HPA axis abnormalities in patients with Alzheimer's disease with a broader range of behavioral disturbances.

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# Frontal, Temporal, and Striatal Proton Relaxation Times in Schizophrenic Patients and Normal Comparison Subjects

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*Spin-lattice ($T_1$) and spin-spin ($T_2$) magnetic resonance relaxation times were examined in frontal, temporal, and striatal regions of 24 patients with schizophrenia and 10 normal comparison subjects. The schizophrenic patients had more prolonged $T_2$ values than did the comparison subjects, particularly in the left temporal cortex and white matter, suggesting tissue pathology.*

(Am J Psychiatry 1992; 149:549–551)

Spin-lattice ($T_1$) and spin-spin ($T_2$) magnetic resonance relaxation times have been regarded as superior to CT scan Hounsfield numbers in characterizing tissue abnormalities (1). Detectable abnormalities, determined by relaxation time measurements, can also be present even with normal results on gross examination of the magnetic resonance imaging (MRI) scan (2). However, studies in schizophrenic patients have generally measured only $T_1$ values and have shown inconsistent results (3). Part of these differences may be related to the precision of the $T_1$ measure. We have previously found prolonged $T_2$ relaxation times in the left dorsolateral cortex in association with negative symptoms in schizophrenic patients (4). $T_2$ values in this study showed much less variability and may have been more sensitive to pathological change.

The purpose of the present investigation was to examine both $T_1$ and $T_2$ relaxation times in schizophrenic patients and in normal subjects. Because evidence from a number of sources has implicated involvement of the frontal lobes, basal ganglia, and temporal lobes in schizophrenia (5), we hypothesized that $T_2$ relaxation times would be prolonged in these regions.

## METHOD

### *Subjects*

Twenty-four schizophrenic patients (22 men and two women) between the ages of 25 and 53 (mean=36.8, SD=7.1) volunteered to participate in the study. All were outpatients receiving depot neuroleptic medications; their mean chlorpromazine-equivalent dose was 631.3 mg/day (SD=502.7). The diagnosis of schizophrenia was confirmed by a psychiatrist (P.W.) using the Structured Clinical Interview for DSM-III-R (6). An average of 14.0 years (SD=5.7) had elapsed since the onset of symptoms in this group. All but one patient reported that they wrote and threw a ball with their right hand. None of the patients was found to have a history of head injury, drug or alcohol abuse, or serious medical illness. One patient reported a history of three seizures before the age of 8. He was not treated with anticonvulsants. None of the patients was taking medication other than the neuroleptic plus, in some patients, antiparkinsonian medication.

Ten normal subjects (nine men and one woman) between the ages of 21 and 47 (mean=32.0, SD=8.5) also volunteered to participate in the study. Each was interviewed by a psychiatrist (P.W.) using the Structured Clinical Interview for normal subjects (6). All but one subject reported that they wrote and threw a ball with their right hand. None had a history of psychiatric illness, head injury, drug or alcohol abuse, or serious medical illness. None of these subjects was taking medication of any type. Informed consent was obtained from all subjects in both groups.

### *MRI*

MRI scans were performed with a GE 1.5-T Signa system. A TR 400 TE20 "scout" sagittal image was used to set up the 13-slice, 5-mm thick, 5-mm gap coronal spin echo acquisitions: the first a TR600 TE20 and the second a TR2000 TE20, 40, 60, and 80. The field of view was 20 cm; the matrix was 256 by 128; there were two excitations for each of the 128 phase-encoded steps. One technician performed all of the scans. This technician placed 3-mm by 3-mm regions of interest to obtain the average $T_1$ and $T_2$ for the dorsolateral prefrontal cortex, middle frontal lobe white matter, temporal cortex, medial temporal lobe white matter, and lenticular

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**TABLE 1. $T_1$ and $T_2$ Relaxation Times in Frontal and Temporal Regions and Basal Ganglia of 24 Schizophrenic Patients and 10 Normal Comparison Subjects**

| | Left | | | | Right | | | |
|---|---|---|---|---|---|---|---|---|
| | $T_1$ | | $T_2$ | | $T_1$ | | $T_2$ | |
| Region and Subjects | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Frontal region | | | | | | | | |
| Dorsolateral prefrontal cortex | | | | | | | | |
| Normal subjects | 1594 | 265 | 61.1 | 3.0 | 1473 | 267 | 61.7 | 1.8 |
| Schizophrenic patients | 1611 | 301 | 63.3 | 4.6 | 1436 | 285 | 63.9 | 7.0 |
| White matter[a] | | | | | | | | |
| Normal subjects | 658 | 32 | 52.7 | 2.0 | 681 | 59 | 54.5 | 2.1 |
| Schizophrenic patients | 711 | 82 | 55.5 | 2.3 | 690 | 59 | 54.3 | 2.6 |
| Temporal region | | | | | | | | |
| Cortex[b] | | | | | | | | |
| Normal subjects | 1257 | 205 | 60.5 | 2.2 | 1298 | 255 | 61.4 | 4.2 |
| Schizophrenic patients | 1429 | 227 | 65.1 | 3.8 | 1296 | 210 | 63.2 | 4.9 |
| White matter[c] | | | | | | | | |
| Normal subjects | 632 | 30 | 50.5 | 1.9 | 661 | 27 | 52.9 | 1.5 |
| Schizophrenic patients | 677 | 99 | 55.0 | 2.6 | 658 | 70 | 54.0 | 3.1 |
| Hippocampus[d] | | | | | | | | |
| Normal subjects | 1276 | 152 | 60.3 | 3.5 | 1324 | 196 | 60.6 | 3.3 |
| Schizophrenic patients | 1405 | 230 | 64.5 | 5.6 | 1314 | 183 | 63.6 | 4.4 |
| Basal ganglia: lenticular nuclei[e] | | | | | | | | |
| Normal subjects | 955 | 70 | 48.4 | 1.1 | 941 | 30 | 49.9 | 2.6 |
| Schizophrenic patients | 1042 | 104 | 51.4 | 3.1 | 979 | 82 | 49.1 | 3.8 |

[a] Significant difference between schizophrenic patients and normal subjects in left $T_1$ (U=181, p=0.02) and $T_2$ (U=214, p=0.0004); the difference for $T_2$ remained significant after adjustment for multiple comparisons.

[b] Significant difference between schizophrenic patients and normal subjects in left $T_1$ (U=175, p=0.04) and $T_2$ (U=200, p=0.003); the difference for $T_2$ remained significant after adjustment for multiple comparisons.

[c] Significant difference between schizophrenic patients and normal subjects in left $T_1$ (U=167, p=0.08) and $T_2$ (U=217.5, p=0.0003); the difference for $T_2$ remained significant after adjustment for multiple comparisons.

[d] Significant difference between schizophrenic patients and normal subjects in left $T_2$ (U=181.5, p=0.02). Significant difference between schizophrenic patients and normal subjects in right $T_2$ (U=176.5, p=0.03).

[e] Significant difference between schizophrenic patients and normal subjects in left $T_1$ (U=183, p=0.02) and $T_2$ (U=204.5, p=0.001); the difference for $T_2$ remained significant after adjustment for multiple comparisons.

nuclei on both sides, as in our previous study (4). A region of interest in the hippocampus posterior and medial to the amygdala was also selected on both sides for this study. To check the technician's consistency in positioning the regions of interest, the $T_1$ and $T_2$ analyses were repeated on the same images and resulted in mean differences of 4.0% in $T_1$ and 1.2% in $T_2$. To test the long-term $T_2$ precision of the system, a uniform phantom head inside a coil loader was imaged with the same $T_2$ protocol that was used for the test subjects each month. The $T_2$ measures with a region of interest enclosing most of the phantom head varied from 170 to 154 (SD=6); there was no long-term drift in values.

Ventricular size was rated by visual examination of the images by a radiologist (D.P.) who was unaware of relevant data in the study, apart from group assignment. Ventricular size was rated on a 3-point scale on which 0 indicated normal size and 2 indicated the largest ventricles of the group. Similar techniques have been shown to provide reliable estimates of ventricular size in a previous study (7).

### *Analysis*

A conservative approach was taken to analysis in view of the number of comparisons involved. Differences between groups were assessed with the Mann-Whitney U test because a normal distribution was not assumed. Probability values are for two-tailed tests. Assuming that alpha=0.05, a significant difference with 12 related comparisons would require a probability of less than 0.004 (Bonferroni procedure).

## RESULTS

Gross examination of the MRI scans was generally unremarkable and has been described in detail in our previous report on MRI scans in schizophrenic patients (4). Eleven of the 24 schizophrenic patients had a ventricular size rating of 1 or 2. No significant abnormalities were found in the normal subjects, apart from a finding in one subject of greater signal intensity in $T_2$-weighted images in the right temporal lobe, thought to be not clinically significant. The ventricular size ratings in the comparison group were all normal with the exception of one patient who had a rating of 1.

Table 1 shows the differences in $T_1$ and $T_2$ between normal subjects and patients. Higher values of $T_2$ are evident in the schizophrenic patients, particularly in the left frontal white matter, left temporal cortex and white matter, and left lenticular nucleus. There are fewer differences on the right side or in frontal cortical regions. A single $T_2$ measurement in the right frontal cortex in a normal comparison subject was not included in the mean in this table because the original image data were accidentally erased. The left frontal white matter, left temporal cortex, left temporal white matter, and left lenticular differences remained significantly different from those of the schizophrenic patients at p=0.004, allowing for multiple comparisons. There was no difference in $T_2$ values between schizophrenic patients with and without ventricular enlargement at any location demonstrating a difference from normal subjects.

Higher $T_1$ values were found in schizophrenic patients than in normal subjects in the left frontal white matter, left temporal cortex, left temporal white matter, and left lenticular nucleus (table 1). However, the standard deviations for these values were generally much higher than those found with $T_2$ values. None of these values was significant after allowing for multiple comparisons, although they may well represent a weak but meaningful trend in the same direction as the more definite $T_2$ findings.

## DISCUSSION

This study demonstrates longer $T_2$ relaxation times, particularly in left temporal regions, in schizophrenic patients than in normal subjects. We are aware of only preliminary data (8) on six patients reporting a similar difference in $T_2$ values in the left temporal white matter. It is intriguing that these areas correspond to those found to be smaller in volume by an earlier study (9). The finding of prolonged relaxation times suggests that tissue differences as well as volumetric differences occur in this region in schizophrenic patients. The $T_2$ differences found in the left frontal white matter and lenticular nucleus of schizophrenic patients compared with normal subjects are in keeping with those from many other imaging techniques (5). Although there were no differences between patients and normal subjects in the frontal cortex, the elevated $T_2$ values seen with negative symptoms in patients in our earlier study (4) were much higher than the means of the normal subjects in this study.

$T_1$ and $T_2$ relaxation times depend on protons in macromolecules, mobile fatty acids, and bound and free water, along with the exchange rates among these compartments (10, 11). Various pathological processes influence these measures directly and therefore alter $T_1$ and $T_2$, but changes in $T_1$ and $T_2$ are not specific to any particular pathological condition (10). Recent in vitro findings (12, 13) suggest that changes in $T_1$ and $T_2$ are not caused by changes in the water compartments but by changes in the cell structure. One possibility is that changes in cell membranes alter $T_1$ and $T_2$ values (13, 14). This would be in keeping with membrane changes reported in schizophrenia with magnetic resonance spectroscopy (15, 16).

A number of limitations must be acknowledged in this study. Lack of field homogeneity, from slice to slice and within a slice, was a problem that was minimized by placing regions of interest at the same location in the same slice. Therefore, $T_2$ values tended to be similar in comparable regions with relatively low standard deviations between subjects. Repeated analysis in one subject demonstrated a high degree of reliability. Partial volume effects were minimized with small regions of interest and consistent image slice location from the "scout" image. There were also no differences in $T_2$ between patients with and without ventricular enlargement. Medication effects cannot be completely ruled out but seem unlikely because differences were not seen in many frontal and right-sided locations.

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CLINICAL AND RESEARCH REPORTS

# Past Substance Abuse and Clinical Course of Schizophrenia

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*To evaluate the effects of previous alcohol and drug use on the course and symptoms of schizophrenia, the authors compared 34 patients with schizophrenia who had histories of substance abuse with 17 patients with schizophrenia who were lifelong abstainers. Surprisingly, they did not find that individuals with past histories of abuse were more impaired or had more symptoms.*

(Am J Psychiatry 1992; 149:552–553)

Although the frequent co-occurrence of schizophrenia and substance abuse is well established (1), the net effect of substance abuse on the long-term course of schizophrenia has not been determined (2). Most studies have concentrated on the acute effects of substance use and have found that patients with schizophrenia who met criteria for current substance abuse had more symptoms, were more impaired, and were more treatment resistant than patients who did not abuse substances (3–5). However, some investigators have noted potential benefits of specific substances, such as amphetamines improving negative symptoms (6) and cocaine enhancing attention (5).

To investigate a group of patients with "pure" schizophrenia, we designed a study with restrictive entrance criteria that excluded patients if they had *ever* abused alcohol or psychoactive street drugs. Unfortunately, patient enrollment was severely limited because so many of the schizophrenic patients available to us had either past or present histories of substance abuse. It became clear that the results of the study might be compromised by the small number of patients in the study as well as the lack of generalizability to all patients with schizophrenia, many of whom use and abuse various drugs (1). Therefore, we initiated the current study to compare the clinical characteristics of subgroups of schizophrenic outpatients with and without past histories of substance abuse.

## METHOD

Informed consent was obtained from 65 subjects who met *DSM-III-R* criteria for schizophrenia, were medically stable, and did not meet criteria for any other axis I diagnosis (including alcohol or other substance abuse within 6 months of study entry). A detailed history of the frequency and quantity of all psychoactive and illegal substances was obtained from subjects and corroborated by chart review, medical records, and interviews with relatives whenever possible.

Since *DSM-III-R* criteria for substance abuse are based largely on psychosocial impairment, they are difficult to apply to schizophrenic patients. Consequently, we developed our own operational criteria for substance use. To be classified as an "abstainer," a patient had to meet the following criteria: 1) never consumed more than five alcoholic drinks on any one occasion, 2) never consumed alcohol on more than 3 consecutive days, and 3) never experimented with marijuana or other substances of abuse. Of the 65 patients who entered the study, 17 (26%) were classified as "abstainers." The 34 (52%) who were classified as "past substance abusers" met at least one of the following criteria 6 or more months before the intake assessment: 1) drank more than five alcoholic beverages per day at least 5 days a week over any 6-month period of time, 2) smoked more than one marijuana cigarette per day at least 5 days a week over any 6-month period of time, 3) reported more than 30 occasions of illegal drug use other than marijuana over their life span. The remaining 14 (22%) patients had histories of substance use but did not meet criteria for abstinence or past abuse.

## RESULTS

The most commonly used substance was marijuana, followed by alcohol; use of amphetamines and hallu-

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cinogens was considerably less common. The majority of patients had used more than one substance. Only seven (41%) of the 17 abstainers were men, compared with 26 (77%) of the 34 past substance abusers ($\chi^2$= 6.18, df=1, $p<0.01$). The abstainers and past abusers were similar in mean age (28.8 years [SD=7.9] versus 30.3 years [SD=7.7], respectively) and amount of education (13.8 years [SD=1.7] versus 12.9 years [SD=1.7]). However, the abstainers were significantly younger at the time of their first psychiatric contact (17.8 years [SD=4.8] versus 21.3 years [SD=5.5], t=2.33, df=36, $p<0.05$). The two groups did not differ in mean number or length of hospitalizations or medication doses; nor did they differ on the percentages of individuals who were married, living alone, receiving disability, or working. Although there were no significant differences between the groups on total Brief Psychiatric Rating Scale (BPRS) (7) scores or on the three-item BPRS depression cluster, there was a trend for the abstainers to have higher scores on the BPRS thought disorder cluster (8.7 [SD=4.3] versus 6.4 [SD=3.6], t=1.87, df=28, p= 0.07). Total global scores on the Scale for the Assessment of Positive Symptoms (8) were also higher in the abstinent group (8.2 [SD=2.8] versus 5.6 [SD=4.7], t= 2.43, df=47, $p<0.05$), but total global scores on the Scale for the Assessment of Negative Symptoms (8) were not significantly different. Finally, the abstainers had a significantly higher percentage of subjects who were subtyped as "disorganized" than did the past abusers (41% [N=7] versus 18% [N=6], $\chi^2$=6.03, df=2, $p<0.05$). Although the lack of more differences between the two groups may be related to the small number of subjects (type II error), the associated probabilities for most analyses did not even approach significance.

## DISCUSSION

Contrary to our initial hypothesis, schizophrenic patients with past histories of substance abuse did not have more symptoms and were not more impaired than schizophrenic patients who had never abused drugs. Indeed, the groups were similar on most demographic, historical, clinical, and outcome variables. If anything, the schizophrenic patients with past histories of substance abuse appeared "healthier" in that they had less severe thought disorders and positive symptoms, were less likely to be described as disorganized, and were older at the time of their first psychiatric contact. It may be that these individuals, who were able to stop their substance abuse, possess other attributes that could ultimately contribute to a better prognostic outcome.

This study should *not* be interpreted as suggesting any benefits to patients with schizophrenia from substance abuse. We have no way of knowing how the abused substances may have affected the lives or the course of illness of the abusing patients with schizophrenia. Indeed, these patients may be functioning at lower levels than if they had remained drug-free throughout their lives. Further, we feel certain that had we studied subjects who were *currently* abusing drugs, the results would have been quite different. However, these results suggest that a history of substance abuse does not necessarily interact with schizophrenia to yield a particularly malignant or intractable form of the illness (9). After 6 months of abstinence, schizophrenic outpatients who kept their substance abuse under control were doing at least as well as patients with schizophrenia who had never abused alcohol or drugs. These results may be consistent with a recent community survey suggesting that some drug use is more "normal" than total abstinence (10) and with an inpatient study showing more improvement in past and present abusers than in nonabusers during hospitalization (9). Many of the abstainers in this study, especially those with the virulent subtype of disorganized schizophrenia, may have been too socially withdrawn or disorganized to have been exposed to drugs or the social situations that encourage experimentation during adolescence. Further prospective studies using larger numbers of patients are needed to enhance our understanding of how substance abuse affects the course of schizophrenia.

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# Comorbidity in Mania at First Hospitalization

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*Comorbidity was studied in 41 manic and mixed-state bipolar patients at first hospitalization. The lifetime prevalence of comorbidity was high; 21 subjects (51.2%) had at least one other psychiatric diagnosis (N=16, 39.0%) or medical disorder (N=9, 22.0%). Nine subjects had multiple comorbid diagnoses. Women were 2.7 times more likely to have a comorbid diagnosis. The presence of comorbidity was not associated with differences in outcome measures.*

(Am J Psychiatry 1992; 149:554–556)

In 1978, Krauthammer and Klerman (1) reported 21 cases of mania associated with medical or pharmacologic conditions and proposed the existence of secondary mania. Later, Cummings (2) reviewed mania associated with various medical conditions. Black et al. (3) defined complicated mania as "manic syndromes occurring in the context of antecedent or coexistent psychiatric disorders or a concurrent serious medical disorder." They retrospectively studied 57 patients with complicated mania and 114 subjects with uncomplicated mania, who were matched by age, sex, and year of admission and were drawn from a larger cohort of 438 patients with mania. They observed significant differences in demographic variables between groups and poorer initial treatment response in the group with complicated mania (3). Stimulated by these reports, we sought to clarify further the relationship between mania and comorbidity and now report on the risks of comorbidity in bipolar manic patients at first psychiatric hospitalization.

## METHOD

Patients 18 years or older who were consecutively admitted for a first psychiatric hospitalization with manic symptoms were approached for participation in this study. Subjects who met *DSM-III-R* criteria for bipolar disorder, manic or mixed, and provided informed consent were included. Patients were not excluded because of the presence of possible organic precipitants (*DSM-III-R* mania criterion F). Diagnostic assessments were made with the Structured Clinical Interview for *DSM-III-R* (4); after completion each interview was reviewed by a second investigator (S.M.S.). Medical diagnoses were established through patient examinations and review of the medical record. Comorbidity (complicated mania) was defined after Black et al. (3) as the presence of nonaffective *DSM-III-R* axis I psychiatric diagnoses or serious or potentially life-threatening medical illnesses, such as cancer and myocardial infarction, but not well-controlled conditions, such as chronic hypertension.

Weekly assessments were made with the Clinical Global Impression scale (CGI) (5) and an expanded 27-item Brief Psychiatric Rating Scale (BPRS) (6) that included the following nine additional items: speech, euphoria, increased motor activity, sexual interest, sleep, insight, suicidal thoughts, appetite, and dysphoria. In addition, each *DSM-III-R* criterion for mania and major depression was scored on a 1- to 7-point scale of severity, as for the CGI. Treatment was determined clinically and was not controlled by the investigators. Outcome variables were length of hospitalization, change in BPRS score, final CGI score, and antipsychotic drug use at discharge. Recovery from mania was defined as a CGI score of 2 or less (2=very mildly ill), a rating of 3 or less on the *DSM-III-R* mania A criterion, no B criterion rated higher than 3, and no more than two B criteria rated equal to 3. Recovery from depression was defined as a CGI score of 2 or less, no *DSM-III-R* depression criterion rated higher than 3, and no more than three depression criteria rated equal to 3.

Nonparametric statistical analysis was performed. Categorical variables were compared by using the one-tailed Fisher exact test; continuous variables were evaluated by using the Wilcoxon rank sum test.

## RESULTS

Forty-one bipolar subjects met criteria for inclusion; 33 (80.5%) were manic and eight (19.5%) were in a

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**TABLE 1. Comorbid *DSM-III-R* Diagnoses in Patients With First-Episode Mania[a]**

| | Women (N=25) | | Men (N=16) | | With Substance Abuse (N=11) | | Without Substance Abuse (N=30) | | Total (N=41) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Comorbid Diagnosis | N | % | N | % | N | % | N | % | N | % |
| None[b] | 8 | 32.0 | 12 | 75.0 | | | 20 | 66.7 | 20 | 48.8 |
| Psychiatric | 14 | 56.0 | 2 | 12.5 | 11 | 100.0 | 5 | 16.7 | 16 | 39.0 |
| Alcohol abuse or dependence[c] | 9 | 36.0 | 1 | 6.3 | 10 | 90.9 | | | 10 | 24.4 |
| Drug abuse or dependence[c] | 6 | 24.0 | 1 | 6.3 | 7 | 63.6 | | | 7 | 17.1 |
| Obsessive-compulsive disorder | 2 | 8.0 | 1 | 6.3 | 2 | 18.2 | 1 | 3.3 | 3 | 7.3 |
| Bulimia nervosa | 3 | 12.0 | 0 | 0.0 | 1 | 9.1 | 2 | 6.7 | 3 | 7.3 |
| Simple phobia | 1 | 4.0 | 1 | 6.3 | 1 | 9.1 | 1 | 3.3 | 2 | 4.9 |
| Panic disorder | 2 | 8.0 | 0 | 0.0 | 1 | 9.1 | 1 | 3.3 | 2 | 4.9 |
| Agoraphobia without panic | 1 | 4.0 | 0 | 0.0 | 1 | 9.1 | 0 | 0.0 | 1 | 2.4 |
| Medical | 7 | 28.0 | 2 | 12.5 | 3 | 27.3 | 6 | 20.0 | 9 | 22.0 |
| Pneumonia[d] | 3 | 12.0 | 0 | 0.0 | 1 | 9.1 | 2 | 6.7 | 3 | 7.3 |
| Prednisone exposure[e] | 1 | 4.0 | 1 | 6.3 | 1 | 9.1 | 1 | 3.3 | 2 | 4.9 |
| Acute congestive heart failure | 0 | 0.0 | 1 | 6.3 | 0 | 0.0 | 1 | 3.3 | 1 | 2.4 |
| Cerebral palsy | 1 | 4.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.0 | 1 | 2.4 |
| Hypothyroidism | 1 | 4.0 | 0 | 0.0 | 1 | 9.1 | 0 | 0.0 | 1 | 2.4 |
| Temporal lobe epilepsy | 1 | 4.0 | 0 | 0.0 | 0 | 0.0 | 1 | 3.3 | 1 | 2.4 |

[a] Nine subjects had more than one diagnosis.

[b] Significant difference between sexes (p=0.008, Fisher's exact test).

[c] Significant difference between sexes for any substance abuse (p=0.02, Fisher's exact test).

[d] One patient had pneumonia with an acute asthmatic exacerbation.

[e] One patient received prednisone for an exacerbation of Reiter's syndrome; the other for an allergic rash to imipramine 3 weeks previously.

mixed manic-depressive state. The mixed-state patients averaged 10.9 years older than the manic patients (mean ages=40.4 years, SD=11.7, versus 29.5, SD=12.7; Z=2.42, p=0.02) but otherwise showed no differences in demographic, comorbidity, or outcome variables. Twenty-five subjects (61.0%) were women; they averaged 8.0 years younger than the men, a difference that did not reach statistical significance (mean=28.5 years, SD=9.1, versus mean=36.5, SD=16.8; Z=1.11, p=0.27). Comorbidity, or complicated mania, was present in 21 (51.2%) of the subjects, including 16 (39.0%) with another antecedent or concurrent axis I psychiatric disorder and nine (22.0%) with concurrent medical illness. More than one comorbid diagnosis was present in nine subjects (22.0% of the total). Women had a 2.7-fold higher rate of comorbidity (17 of 25 women [68.0%] versus four of 16 men [25.0%]; p=0.008, Fisher's exact test). No significant differences between patients with complicated and uncomplicated mania were observed in age (mean=32.2 years, SD=10.0, versus mean=30.4, SD=16.0; Z=–1.45, p=0.15), length of hospitalization (mean=34.3 days, SD=15.4, versus mean=37.0, SD=16.7; Z=0.57, p=0.57), change in BPRS score (mean=30.3, SD=16.2, versus mean=31.2, SD=19.8; Z=0.16, p=0.88), final CGI score (mean=2.1, SD=1.1, versus mean=2.1, SD=1.1; Z=–0.15, p=0.88), number of subjects taking antipsychotic medication at discharge (13 of 21 versus 14 of 20; p=0.42, Fisher's exact test), or recovery rate (12 of 21 patients versus 14 of 20 patients; p=0.30, Fisher's exact test).

Specific comorbid diagnoses are listed in table 1. Women were 6.4 times more likely to have a history of comorbid substance abuse or dependence (10 of 25 women [40.0%] versus one of 16 men [6.3%]; p=0.02, Fisher's exact test). Subjects with a history of drug abuse or dependence were 3.2 times more likely to have another comorbid psychiatric diagnosis (six of seven with drug abuse or dependence [85.7%] versus nine of 34 without [26.5%]; p=0.006, Fisher's exact test). A similar association was noted for alcohol abuse or dependence (six of 10 with alcohol abuse or dependence [60.0%] versus six of 31 without [19.4%]; p=0.02, Fisher's exact test) (table 1). Of the nine subjects with medical comorbidity, three had chronic, stable illnesses (cerebral palsy, treated hypothyroidism, and temporal lobe epilepsy), and six had acute illnesses or acute exacerbations of chronic medical conditions (table 1). The six subjects with concurrent acute medical conditions averaged 10.3 years older than the other 35 subjects (mean=40.4 years, SD=11.2, versus mean=30.1, SD=12.9; Z=2.12, p=0.03), were 4.4 times less likely to have antipsychotic medication prescribed at discharge (one of six subjects [16.7%] versus 26 of 35 subjects [74.3%]; p=0.01, Fisher's exact test), and had a hospitalization that was 34% shorter (mean=24.8 days, SD=7.3, versus mean=37.5, SD=16.3; Z=–1.90, p=0.06).

## DISCUSSION

To our knowledge, this is the first study to examine comorbidity in mania at the time of first hospitalization. Complicated mania was nearly four times more prevalent in our cohort of 41 consecutively admitted bipolar patients than in the group reported by Black et al. (3). Further, unlike that study, we did not observe significant differences in early clinical outcome between groups with complicated and uncomplicated mania.

These discrepancies likely reflect methodologic differences. Whereas the study by Black et al. (3) used retrospective chart reviews, thereby relying on the clinical recording of diagnoses (both axis I and axis II) and outcome variables, the present study was prospectively designed with structured diagnostic patient interviews (for axis I), review of current treatment records, and recovery operationally defined from clinical ratings. These significant methodologic differences limit the comparability of the two studies.

The most common comorbid diagnoses in the present study were alcohol and drug abuse or dependence. It has been suggested that bipolar patients may abuse substances to self-medicate their affective symptoms or that substance abuse may precipitate or perpetuate affective episodes (7). Conversely, primary substance abusers frequently demonstrate affective psychopathology, and substance abuse is known to produce significant affective symptoms (8). In fact, in all but one subject the onset of substance abuse preceded hospitalization by more than 1 year. However, possible prodromal affective symptoms predating or concurrent with the onset of substance abuse could not be reliably determined in the present cohort, limiting conclusions that can be drawn. The reasons for the nearly threefold higher rate of comorbidity among women, much of which was due to substance abuse, are unclear. Whether this may reflect differences between men and women in reporting past histories of substance abuse requires further study.

Concurrent acute medical conditions in our cohort were associated with older age, less likelihood of antipsychotic medication being prescribed at discharge, and a trend toward a shorter hospitalization. Whether this small subgroup represents mania resulting from medical conditions, so-called secondary mania, rather than expressions of primary bipolar disorder requires further study.

Several diagnoses appeared to be more common in the present cohort than in the general population, compared to the lifetime prevalence reported by the recent Epidemiologic Catchment Area study (9). These diagnoses included alcohol abuse or dependence (24.4% versus 13.5%), drug abuse or dependence (17.1% versus 6.1%), obsessive-compulsive disorder (7.3% versus 2.5%), and panic disorder (4.9% versus 1.6%).

The most significant limitation of this study is the small sample size and limited statistical power; only six subjects had acute medical illnesses. Further, we studied only hospitalized, acute, manic, or mixed-state bipolar patients, limiting the applicability of these results to bipolar disorder in general. Despite its limitations, this study examined an important clinical issue in a unique cohort of bipolar patients at first hospitalization. Our results suggest that the prevalence of comorbidity in bipolar disorder may be higher than previously thought, even early in the course of the illness. Although the long-term effects of comorbidity are uncertain, early identification of additional medical and psychiatric diagnoses is important for the development of appropriate clinical treatment.

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# Associations Between Dimensions of Religious Commitment and Mental Health Reported in the *American Journal of Psychiatry* and *Archives of General Psychiatry:* 1978–1989

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*The authors assessed all measures of religious commitment (N=139) reported in research studies published in the* American Journal of Psychiatry *and* Archives of General Psychiatry *in 1978 through 1989 (N<35). For nearly two-thirds of the measures, the studies either made no hypotheses or reported no results concerning the relationship of religious commitment to mental health status. For the great majority of the measures assessed, the studies reported a positive relationship between religious commitment and mental health.*

Am J Psychiatry 1992; 149:557–559)

There is evidence that religious practices and beliefs are understudied phenomena in clinical fields such as psychiatry (1) and family medicine (2). When religion has been studied, it has usually been assessed by using a static measure—denominational affiliation. Psychiatric studies seldom contain variables reflecting religious commitment, such as measures of religious experience, belief, attitudes, or practice (1).

Studies concerning dimensions of religious commitment have emphasized its multidimensional nature (1–4), including meaning, ceremony and sacramental activities, social support, and relationship with the deity (5). Each of these religious dimensions might have positive or negative relationships to various aspects of clinical status. For instance, there have been some reports of negative or harmful associations between religious commitment and mental health (6), but other reports have detailed positive or beneficial effects (4, 7–10).

A systematic review by Bergin (3) took an important step in clarifying the association between religiousness and mental health. Not only did Bergin find little relationship between religiousness and psychopathology, he also found that religious commitment had a positive association with mental health in nearly half (47%) of the study effects tabulated. In contrast, associations with mental health were neutral in 30% and negative in less than one-fourth (23%) of the tabulated associations.

A recent review by Gartner et al. (8) revealed several interesting trends in research on the relationship between religious commitment and psychopathology or mental health. Most of the studies assessing nonclinical populations (e.g., college students) that used measures of psychopathology not based on psychiatric nosology found religion to have either a neutral or harmful role more often than a positive role. In contrast, studies assessing clinical populations that used measures based on psychiatric nosology found religious commitment to have a beneficial role more often than a harmful role. In addition, studies that included measures of religious practice found religiousness to be associated with mental health benefits more often than did studies including measures of religious attitudes.

Our current study was undertaken to follow up the findings of the review of the field of psychology (3) and the review of the combined mental health field (8) and to provide for psychiatry a state-of-the-art review of associations between religious commitment and mental health. The review entailed the systematic assessment (1, 2) of all religious commitment variables found in research studies published in the two leading psychiatry journals over a 12-year period. Using the method of Craigie et al. (10), we determined whether positive, negative, or neutral associations between mental health and religion were found, hypothesized, or reported. We also tabulated the associations and classified them according to the typology of religious dimensions used by Craigie et al. (10).

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The views expressed in this article are those of the authors and do not necessarily represent the views of NIMH or the U.S. Department of Health and Human Services.

**TABLE 1. Associations Between Dimensions of Religious Commitment and Mental Health Reported in the *American Journal of Psychiatry* and *Archives of General Psychiatry:* 1978–1989**

| | Number of Measures Assessing Dimension of Religious Commitment | | | | | | |
|---|---|---|---|---|---|---|---|
| | Hypothesis of Study | | | Results of Study | | | |
| Dimension of Religious Commitment | Positive Association | Negative Association | None | Positive Association | Negative Association | Neutral Association | Association Not Tested |
| Ceremony | 2 | 0 | 11 | 4 | 0 | 0 | 9 |
| Meaning | 3 | 5 | 34 | 7 | 4 | 0 | 31 |
| Social support | 11 | 1 | 13 | 7 | 0 | 1 | 17 |
| Prayer | 3 | 0 | 13 | 4 | 1 | 0 | 11 |
| Relationship with God | 1 | 0 | 14 | 9 | 0 | 0 | 6 |
| Indeterminate | 1 | 3 | 24 | 5 | 3 | 5 | 15 |
| Total | 21 | 9 | 109 | 36 | 8 | 6 | 89 |

## METHOD

The first step was to locate all quantified religious measures found in research studies published in the *American Journal of Psychiatry* and *Archives of General Psychiatry* in 1978 through 1989. Each religious measure was then categorized into one of the following religious dimensions: 1) ceremony (participation in religious ceremonies, sacraments, or rituals), 2) meaning (personal purpose, values, beliefs, and ethics), 3) social support (use or influence of social support), 4) prayer (prayer or personal religious devotional practices), and 5) relationship with God (issues concerning a personal relationship with God). Because of the ambiguous nature of the remaining measures, a sixth category termed "indeterminate" (e.g., use of the term "religion" or "religiosity" with no further specification) was developed. Measures of denomination were excluded because of their differences with measures of religious commitment (1, 2, 9, 10). Finally, each religious measure was evaluated to discern whether the research study hypothesized a positive or a negative association between religious commitment and mental health and whether a positive, negative, or neutral result was reported.

Interrater reliability was sufficient across all ratings. Using a kappa coefficient, we found that the reliability of all ratings of the association between religious commitment and mental health was 0.89. The reliability for all hypothesized associations between religious commitment and mental health was 0.82, but it was slightly higher—0.93—for all reported associations between religious commitment and mental health. The reliability kappa for ceremony was 0.82; for meaning, 0.82; for social support, 0.82; for prayer, 0.90; for relationship with God, 0.78; and for the indeterminate dimension, 0.76.

## RESULTS

In 1978–1989, all quantified studies in the *American Journal of Psychiatry* and *Archives of General Psychiatry* (N<35) contained 139 quantified religious commitment measures. Table 1 presents the number of measures for which positive or negative associations between mental health and six dimensions of religious commitment were hypothesized, the number of measures for which the hypothesis regarding these associations were not specified, the number of measures for which positive, negative, or neutral associations were reported, and the number of measures for which the association was not tested. Only 30 (22%) of the 139 measures were in studies that hypothesized results concerning religion, and only 12 of these were in studies that later tested the given hypothesis. All seven of the 21 associations that were expected to be positive and were tested turned out to be positive. Five of the nine associations that were expected to be negative were tested, and four of these turned out to be negative.

Although only 12 of the 30 studies with an a priori hypothesis reported an association between religious commitment and mental health, an additional 38 reported such an association even though no hypothesis was given. Thus, for only 50 (36%) of the 139 measures the study reported an association between religious commitment and mental health. Of these 50, 36 (72%) of the associations were positive, eight (16%) were negative, and six (12%) were neutral. As for the dimensional findings, four of the six dimensions (ceremony, social support, prayer, and relationship with God) had uniformly positive, or beneficial, associations (24 of 26, or 92%). The remaining two religious dimensions—meaning and the indeterminate dimension—accounted for seven of the eight negative findings and five of the six neutral findings.

## DISCUSSION

Consistent with several reviews, the present study found that when a religious variable is studied, it often has a positive association with measures of health (4, 10) or mental health (3, 8). Quite similar to the findings of the family medicine review (10), the dimensions of ceremony, social support, prayer, and relationship with God, although seldom assessed, were all found to have positive associations with mental health. More studies clarifying the clinical role of these dimensions, similar to recent studies by Pressman et al. (7) and Williams et al. (9), are needed.

The dimension of meaning appears to have a greater potential for negative associations. This finding is consistent with the reported research in family medicine (10), where only one of 15 studies including this dimension found a positive association with clinical status. Future studies including the dimension of religious meaning need to pay greater attention to precisely defining and accurately measuring religious meaning as well as to evaluating both the negative and the positive effects of this dimension. Given previous research concerning the clinical benefits of religious practices (4, 7–10), a next step would be to look at the associations between clinical variables and high levels of religious meaning combined with low levels of religious practice. For example, subjects attesting to a high meaningfulness of religion but not attending religious services could experience this incongruity as personal conflict, which would result in a negative mental health effect.

That the indeterminate or ambiguous measurement of religion is associated with most of the neutral findings should not be surprising. Inadequate measurement is generally associated with unreliability and the probability of deflated correlations (11).

What is perhaps most surprising is that in the majority of cases in which a religious variable was specified, there were no reported efforts either to formulate hypotheses or to test the association between religious measures and mental health. For only 30 (22%) of the 139 measures was a hypothesis specified. Of these 30, only 12 (40%) reported the results. For only 50 (36%) of the 139 religious measures did the study report findings concerning associations between religious measures and mental health.

Although one can only speculate why the majority of studies neglected to present associations, one possible explanation is that associations were tested, found to be neutral, and, because of their "no effect" status, not reported. Another explanation is that the associations were simply not tested. Unfortunately, in the case of nearly two-thirds of the measures, the studies failed to report any associations whatsoever—whether neutral, positive, or negative—thus leaving important research information for an underdeveloped field of study unaddressed.

In summary, the findings of the present review suggest that religious commitment is a clinically relevant, multidimensional phenomenon with the potential for frequent beneficial and occasional harmful mental health effects. Future research efforts concerning how religious commitment influences mental health status require improvements in research methods. Improvements should include 1) the specification of a priori hypotheses, 2) the accurate measurement of the relevant dimension of religious commitment, and 3) the presentation of the study results concerning the association of religious commitment and mental health status. These improvements are necessary if the next steps are to be taken in this previously neglected but promising area of psychiatric research.

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# International Reliability of a Diagnostic Intake Procedure for Panic Disorder

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*Test-retest diagnostic reliability interviews using the Upjohn version of the Structured Clinical Interview for DSM-III (SCID) were conducted with 72 patients at 13 international sites of the Cross-National Collaborative Panic Study. Agreement on the diagnosis of panic disorder was very good. For the subtypes (uncomplicated, with limited phobic avoidance, and agoraphobia), agreement was fair to good.*

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Initial results from the Cross-National Collaborative Panic Study, a two-phase, multicenter, controlled clinical trial sponsored by the Upjohn Company, have already been reported (1–3). Phase Two of the trial was unique in its geographic scope and compared alprazolam, imipramine, and placebo in patients with panic disorder or agoraphobia with panic attacks in 13 centers in North America, South America, and western Europe. Before the beginning of Phase Two in the summer of 1984, a multicenter reliability study of the diagnostic intake procedure, using the Upjohn version of the Structured Clinical Interview for DSM-III (SCID) (4), was conducted. This report presents the reliability of the diagnosis of panic disorder and its subtypes, as determined in that study.

## METHOD

Each country that was participating in the treatment study agreed to participate in the reliability study as well. The Upjohn version of the SCID was created specifically for this study. It contains an overview and a diagnostic section for panic disorder and its subtypes as well as sections for disorders to be ruled out. Training on the Upjohn version of the SCID took place over approximately 2 days during a general meeting of the Phase Two investigators in November 1983. Videotapes were used to demonstrate correct interviewing techniques, and direct interviews of the participants were observed by trainers from the Biometrics Research Department of New York State Psychiatric Institute.

The "test-retest-interview" method (rather than the "joint-interview" method) of assessing interrater reliability was chosen for this study because it most closely approximates the model of interchangeable interviewers. According to this method, a reliable diagnosis is one that can be made in the same subjects by different interviewers. Although it would have been ideal to select the pairs of interviewers in random order, the participants' busy clinical schedules made this impossible. Therefore, interviewers were selected on the basis of who was available when a particular patient needed to be evaluated. The test-retest evaluations were, ideally, to be the first contact with that patient for each of the two clinicians in the interviewing pair. If there was additional information about the patient from a referral note or the initial screening, it was made available to both clinicians in written form, so that both evaluations were based on the same data to the extent possible. The retest evaluation was completed by the second clinician as soon as possible after the first evaluation to minimize the possibility of the patient's condition changing between the two interviews.

All patients were prescreened over the telephone by a research assistant to ensure that they were suffering from some symptoms of panic disorder, even though they may not actually have had the diagnosis. Patients were randomly selected for test-retest evaluations from everyone who passed through the initial screen. The inclusion criteria for the Phase Two treatment study specified having a diagnosis of panic disorder, agoraphobia with panic attacks, or panic disorder and limited phobic avoidance that was not severe enough to meet the criteria for agoraphobia. All patients were between the ages of 18 and 64 and were in good physical health; they were excluded if they had current symptoms of psychosis, suicidality, or dementia or a history of bipolar, cyclothymic, or obsessive-compulsive disorder, seizures, melancholia, or drug or alcohol depend-

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ence. Patients currently in psychotherapy or behavior therapy were also excluded.

When an interview was completed, each clinician independently completed an Upjohn version of the SCID diagnostic score sheet. Data analysis was conducted by the Biometrics Research Department. Tests from all sites were analyzed together to estimate the reliability of the international participants as one study team.

## RESULTS

Thirteen sites in 11 countries participated in this study: Belgium, Brazil, Canada, Colombia, France, Mexico, Spain, the United Kingdom, the United States, Germany, and Austria. Countries contributed from one to 19 test-retest interview pairs; the mean was 7; on average, five clinicians per country participated in this study. Altogether, 72 patients were evaluated; 52 (72%) were retested within 1 week of the first interview (range=0–40 days).

Table 1 presents the kappa coefficients of agreements for the diagnostic category of panic disorder and its three subtypes. Agreement on the diagnosis of panic disorder was very good. For the subtypes, within the group of patients who were diagnosed as having panic disorder, agreement was fair to good.

**TABLE 1. Agreement and Disagreement on Diagnoses of Panic Disorder and Its Subtypes by Interviewers in 13 International Sites**

| Diagnosis | Agreements | | Disagreements | Kappa |
|---|---|---|---|---|
| | Positive | Negative | | |
| Panic disorder | 62 | 8 | 2 | 0.87 |
| Subtypes | | | | |
| Uncomplicated | 9 | 47 | 5 | 0.73 |
| With limited phobic avoidance | 24 | 25 | 12 | 0.61 |
| Agoraphobia with panic attacks | 15 | 37 | 9 | 0.66 |

## DISCUSSION

This was the first international diagnostic reliability study within a clinical trial (here, the Cross-National Collaborative Panic Study). Interviews of a series of patients each evaluated by two clinicians on separate occasions (test-retest reliability) demonstrated very good agreement for panic disorder and fair to good agreement for its subtypes.

In an NIMH-funded multisite reliability study of a later version of the full SCID (modified for *DSM-III-R*), kappas of 0.58 and 0.59 were obtained for 390 psychiatric patients and 202 nonpatients, respectively, for the diagnosis of panic disorder (5). These are somewhat lower than in the current study, probably because there was no prescreening of subjects and no specific focus on panic disorder; all diagnoses in the full SCID were assessed.

Using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA), a clinical interview guide designed to focus specifically on anxiety disorders, Mannuzza et al. (6) obtained a kappa of 0.79 on evaluations of 104 patients in an anxiety disorder clinic. Their kappas for the subtypes were 0.76 for uncomplicated, 0.62 for limited phobic avoidance, and 0.81 for agoraphobia. These kappas, and those in the present study, are relatively high, undoubtedly because both studies focused on anxiety disorders and because patients were prescreened.

Maier et al. (7) interviewed 40 consecutive inpatients with depressive and/or anxiety syndromes using the Upjohn version of the SCID in a test-retest design. The kappa for panic disorder (N=12) was 0.83, and the kappa for "panic disorder, with avoidance behavior" (N=11) was 0.53. Since both of these kappas were statistically significantly higher than corresponding kappas obtained from the test-retest administration of a diagnostic checklist (0.66 and 0.48, respectively), the authors concluded that "the application of structured clinical interviews in clinical trials for the evaluation of . . . anxiety disorders (*DSM-III*) is clearly recommended by these data."

We conclude that very good diagnostic reliability for panic disorder can be obtained with a structured interview guide in patients who have been prescreened and determined to have anxiety disorders. In nonpatients and general samples of patients, however, agreement is only fair. Future research should be directed toward improving agreement in unselected samples.

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## Information on APA Periodicals at the 1992 Annual Meeting

*American Journal of Psychiatry* staff will be located in the APA Resource Center and the editorial office in Room 19, Level 1, Convention Center. Hours of operation: Saturday, May 2, noon–5:00 p.m.; Sunday, May 3, 10:00 a.m.–5:00 p.m.; Monday, May 4, through Thursday, May 7, 8:00 a.m.–5:00 p.m. Staff at both locations will be available to schedule office appointments with the Editor, answer authors' questions, and receive papers submitted for publication. The *Journal* publishes only original material that has not been published elsewhere in any form and that is not being considered for publication elsewhere. Five copies are required.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

## AFFECTIVE DISORDER

**Psychotherapy for Depression,** *by T. Byram Karasu. Northvale, N.J, Jason Aronson, 1990, 190 pp., $25.00.*

Psychiatry is indebted to Dr. Karasu for his efforts at "rapprochement, both within and across psychologic and pharmacologic domains" (p. vii) and for assembling and summarizing important trends in psychiatric treatment (1). Examples of this include two excellent articles on psychotherapy of depression in the February and March 1990 issues of the *Journal* (2, 3). This book is a handsomely packaged, essentially verbatim reissue of those articles.

The merits of the articles remain. Dr. Karasu succinctly describes three psychotherapeutic approaches to depression: cognitive and interpersonal therapies, whose importance is demonstrated in outcome research, and psychodynamic psychotherapy, widely used by psychiatrists in the United States. In broad strokes he succinctly highlights advantages and limitations of each approach. He raises the crucial, unanswered question of differential therapeutics for depression, a heterogeneous condition without a uniformly ideal treatment. Depression is defined as a spectrum condition spanning dimensions of symptomatology, severity, periodicity, and normality versus pathology—characteristics with presumed implications for treatment. Dr. Karasu concludes with discussions of combining antidepressant pharmacotherapy with each psychotherapy and choosing among and integrating the three psychotherapeutic techniques.

As a Broadway hit may show signs of strain when enlarged on the Hollywood screen, translating these journal articles to book form has introduced tensions. Article paragraph headings have been blown up into chapter titles, each assigned a separate page, and the paragraphs themselves have been developed into brief chapters whose length rarely exceeds three pages. Whereas the articles were long, pithy, admirably crafted epitomes of periodical summation, the identical prose in hard cover can read as breathless and telegraphic. When a paragraph becomes a book chapter, the broad strokes that were strengths of the articles can seem hurried, stretched, overly simplified. For example, generic references to dynamic psychotherapy sometimes leave unclear which model Dr. Karasu has in mind: Luborsky's? Strupp's? Bemporad's? The average clinician's? On page 101, he implies that cognitive therapy and interpersonal therapy are used exclusively for research. Such ellipsis—leading to blank divider pages—may frustrate readers.

The book format offered an opportunity to elaborate on the important issues Dr. Karasu deals with. Largely uncritical descriptions of the psychotherapies might have been developed into fuller critiques. He might have reinforced theory with data from treatment studies and the NIMH Treatment of Depression Collaborative Research Program (4, 5), which give some indication of the relative efficacy and mode specificity or lack of mode specificity of interpersonal therapy and cognitive therapy. For its intended audience of "practitioners" (p. viii), clinical vignettes demonstrating differences in psychotherapeutic approaches might have been helpful.

This text remains a masterly brief overview of three important antidepressant psychotherapies. It will not replace manuals of the treatments it describes but may well whet the reader's appetite for them. It meets its aim "to expand the repertoire of practitioners unfamiliar with some of these approaches and . . . provide a systematic delineation for better communication among them" (p. viii).

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**Animal Models of Depression,** *edited by George F. Koob, Cindy L. Ehlers, and David J. Kupfer. Boston, Birkhäuser (New York, Springer-Verlag, distributor), 1989, 284 pp., $55.00.*

The use of animals in biomedical research continues to be the subject of much controversy and debate. We in the medical community frequently find ourselves faced with opposition from animal rights activists (or "animal rights terrorists," as Secretary Sullivan of the U.S. Department of Health and Human Services, called them in a speech made in Washington, D.C., on June 7, 1990) and the need to justify support for the use of animals in research. There is perhaps no field of medicine more vulnerable to such possible attack than mental illness research. Ultimately, because mental illnesses may be uniquely human disorders, the critical question becomes, Is there anything truly important and meaningful to be learned from animal models?

*Animal Models of Depression* is an important contribution to the field, particularly because of the light it sheds on the promises of animal models in mental disorder research and what it encompasses. The book is a compilation of papers originally presented at a conference in September 1986 on the

Psychobiology of Depression, sponsored by the MacArthur Foundation Research Network. The book follows the outline of the conference and is divided into three sections. The first three chapters present a conceptual overview of animal models in psychiatry. Chapters four to thirteen each present a single study approach using a different animal model. The authors of each of these chapters summarize recent research efforts in the area of study presented and discuss directions for future study. Chapters four to nine present developmental and behavioral models, and chapters ten to thirteen focus on pharmacological models.

Despite the array of contributors, the book is readable, cohesive, and nicely balanced and provides a broad introduction to a number of very different research methodologies. Some of the chapters in the second and third sections may present more detail than the average reader wants to know about specific experimental designs and results. However, because each chapter is self-contained it is easy to pick and choose among topics of interest. In this regard *Animal Models of Depression* is a nice book to have along on a vacation to educate one's self more comprehensively about the rationale, methodology, and progress of different research approaches in the study of depression.

For the clinician who is skeptical about the value of animal models, the first three chapters are especially noteworthy. These chapters discuss from a more theoretical prospective the promises and limitations of animal models and thus provide a foundation from which to approach the rest of the book. In the first chapter McKinney defines animal models as "experimental paradigms developed in one species for the purpose of studying specific aspects of the human illness." He adds, "They are not replicas of human depression in its entirety." The clear consensus that emerges from this book is that there is no one comprehensive animal model for depression and no one best model. Rather, it is argued that different experimental paradigms should be used to investigate different, selected aspects of psychopathology. In the second chapter, Kornetsky nicely distinguishes three types of animal models. He cautions that "a common error is assumption that similar overt behavior [in animals] implies similar [human] mood or experience."

These chapters clearly delineate the potential contributions of animal models to preclinical research. Such models allow greater control and isolation of experimental variables. In addition, the study of parallel processes in animals may spark new research formulations leading to new testable hypotheses and possibly safer, more effective treatments of depression. Although this book focuses on the role of animal models in depression, the theories could be applied just as persuasively to the use of animal models in research on schizophrenia, anxiety disorders, substance abuse, and other mental disorders. In short, *Animal Models of Depression* is a valuable book for clinicians as well as researchers wishing to broaden their scope of understanding of the important contributions of animal models to mental illness research.

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**Depressive Disorders: Facts, Theories, and Treatment Methods,** *edited by Benjamin B. Wolman and George Stricker. New York, John Wiley & Sons, 1990, 424 pp., $49.95.*

This volume is part of the Wiley series on personality processes. The preface of the book explains that the series is directed toward behavioral scientists who have an interest in the theory, measurement, and treatment of human personality.

This particular volume is divided into three major sections: Theories of Depression, Symptomatology, and Diagnostic and Treatment Methods. The chapters in the first section run the gamut of biological, psychodynamic, existential, cognitive-behavioral, psychosocial, and genetic theories. The chapters on symptomatology cover depressive states and somatic symptoms, mood disorders and self-defeating behaviors, symptoms, prevention and treatment of attempted suicide, and levels of depression. The third section consists of chapters dealing with interviewing methods, projective assessment, rating scales, somatic therapies, psychoanalytic therapy, behavior treatments, cognitive therapy, interactional psychotherapy, interpersonal psychotherapy, and marital therapy. Most of the individual chapter authors are well-known in their areas of expertise. The referencing of each chapter is thorough and current through the year of publication (1990). There is an author index, which I found quite useful, as well as a subject index, which although brief covers the material adequately.

In attempting to review this volume, I tried to read it straight through and found this to be a somewhat difficult task. Indeed, it was probably not meant to be used in this manner but, rather, used as a reference base for behavioral scientists interested in depression and, more pointedly, in specific aspects of depression that might be covered in each section. For example, the chapter on interviewing methods gives the background and history of structured interviews and then elaborates in a practical way on a number of interviews used for depression, describing each interview, indicating which affective disorders are diagnosed by the interview, what training is required for administering the interview, how much time the interview takes, etc. Issues relating to reliability and validity for each interview are also discussed.

Some books about mood disorders are written for patients, and some are written for clinicians. This book is likely written for neither group but more for researchers, particularly young researchers who wish to grasp something of the history and theory of mood disorders. As such, the book serves a useful purpose, although its general use may be limited.

One of the striking difficulties with this book is the lack of a uniform or integrated definition of mood disorders. The concept of mood disorder as a personality attribute is given as much weight as is the concept of mood disorder as a medical syndrome. The applicability of personality theories related to mild depressive states needs to be carefully weighed by the reader against descriptions of psychotic depression and bipolar affective disorder. However, given this caveat, the descriptions are quite thorough within each topic and the reader can easily grasp the major concerns of each chapter.

Some of the chapters I found particularly of interest. For example, the chapter on biological theories of depression by Golden and Janowsky is comprehensive in scope, well referenced, and provides an overview of each of the amine theories of depression. Although brief, the chapter presents a level of neurochemistry that would be adequate for someone beginning in the field. The chapter on inventory and rating scales is the most comprehensive on the different ways of measuring depression that I have encountered and would be of interest to many clinicians, at least for the description of each test (MMPI, Hamilton Rating Scale for Depression, Zung Self-Rating Scale, etc.), in terms of what each scale measures, how it is applied, and what is not measured.

This book is a useful reference for investigators interested in depression. I doubt that it would be of interest to patients who suffer from depression or most clinicians who are involved in treating mood disorders. For the researcher, however, it stands as a notable reference text for the decade of the 1990s.

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**Affective and Schizoaffective Disorders: Similarities and Differences,** *edited by A. Marneros and M.T. Tsuang. New York, Springer-Verlag, 1990, 285 pp., $89.70.*

This is an edited volume based on a conference that was a follow-up to an earlier conference, which also resulted in a volume by the same editors (1). In addition to one introductory and two concluding chapters by the editors, this book has 22 chapters, only four of which are from U.S. research teams. Two of the first authors of the other papers come from Great Britain, one from Austria, one from Italy, one from Sweden, one from Switzerland, and 12 from Germany.

This volume has several strengths. Most importantly, it provides an opportunity for monoglot anglophonic psychiatrists to familiarize themselves with diagnostically oriented psychiatric research from European and especially German centers. Furthermore, several chapters of this collected work are particularly noteworthy. Paykel provides a pithy and very well-informed summary of life events research as it applies to affective and schizoaffective disorders. Over three chapters, Marneros and colleagues give an extensive summary of premorbid features, course, and long-term outcome of patients with schizophrenic, schizoaffective, and affective disorders from the Cologne study on the long-term course of functional psychoses. Maier and colleagues provide a brief overview of what appears to be a carefully designed large-sample family study of functional psychosis performed in Mainz, Germany. Tsuang summarizes a thoughtful attempt to empirically validate a proposed subdivision of schizoaffective disorder on the basis of long-term outcome from the Iowa 500 and non-500 series. In one of the more innovative chapters, Coryell attempts to interrelate outcome, neuroendocrine measures, and familial psychopathology in patients with affective, schizoaffective, and schizophrenic disorders. Other chapters, particularly those on treatment, are weaker, being more anecdotal than scholarly in tone and content.

This book has two major weaknesses. First, it suffers from several flaws unfortunately common in edited volumes. There is considerable repetition. For example, the book contains numerous discussions of Kasanin's initial report on schizoaffective disorder (2) and how it relates to current concepts. There is little synthesis of the varying results and perspectives. Although Marneros' final summary chapter is helpful, the disparate chapters need more integration than is provided. Second, it is disappointing that, with a few notable exceptions, most of the authors conducted their studies and reached their conclusions on the basis of a single definition of "schizoaffective disorder." If anything has been shown in research on this problematic category over the last two decades, it is that, depending on the definition of the disorder and/or the method of patient recruitment, it is possible to obtain a syndrome that is either very much like typical affective disorders *or* very much like typical schizophrenia. None of the papers in this volume, for example, examined the *DSM-III-R* criteria for schizoaffective disorder to see whether they succeed at defining a syndrome that is relatively distinct from affective illness.

For those looking to update themselves on European and especially German descriptive psychiatric research on the major functional psychoses, this will prove a useful volume. Those seeking a definitive, integrated review of the relationship of schizoaffective disorder to more typical affective illness will be disappointed.

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**Aging and Clinical Practice: Depression and Coexisting Disease,** *edited by Robert G. Robinson, M.D., and Peter V. Rabins, M.D. New York, Igaku-Shoin, 1989, 233 pp., $29.95 (paper).*

At the outset, I should state that I have a particular interest in the relationships between syndromes of depression and neurological and systemic illness and in the proper care of patients suffering from such co-occurrence of illness. Further, I view these co-occurrences as having a biological foundation that requires biological intervention as a primary treatment strategy.

Although this book generally takes this theoretical tone, it has some clear and serious weaknesses. The editors define their goal as presenting a book that will be 1) a detailed reference source for the "latest research findings" of the relationship between depression and various coexisting neurological and systemic disorders and 2) "a guide for clinical care" of these co-occurring, and in many instances comorbid, combinations. These goals, while salutary, are not fully realized in this volume.

My fundamental criticism of this book is that it was planned to simultaneously aid the primary care physician and the psychiatrist. Unless psychiatric training is less than I think it is and primary care training is more, I cannot conceptualize a book that can be of benefit as a research reference source and a clinical guide to both specialties. For example, how could the prescription and administration of ECT be meaningfully presented simultaneously to both readerships? The book deals with this issue by giving less information about ECT than is usually presented to medical students rotating through their psychiatry clerkship. No clinical guide here. On the other hand, how could a sophisticated review of the latest research be presented to the primary care physician who does not have the background knowledge or a command of the technical language of modern psychiatry to make useful sense of that research?

In my view, in trying to be all things to specialists and generalists, this book becomes unhelpful to both. Despite the importance of the topic and the clear expertise of the many authors involved, this book would suggest that psychiatric clinical skills can be practiced at the state-of-the-art level by nonspecialists. If there is validity to our specialty, we should acknowledge that in the understanding and care of psychiatric patients we have a greater knowledge base and clinical skills than do other specialists, including the primary care physician. A better service to primary care physicians would be either a true how-to-do-it book written at the level of a postgraduate year 1 or 2 psychiatric resident or a registry of competent, medically oriented psychiatric consultants.

Whatever is the reality of the broader issue, this book still does not achieve its goals. The latest literature review is presented, but not in a critical way. Any specialist interested in the topics would be buying a list of references and comments, not an academically or clinically useful discussion of the research. Clear summaries of the latest material are indeed presented, but at a level suitable for the generalist. More importantly, this book fails as a clinical guide. For example, nowhere in this book on depression is there a discussion of the risk factors for suicide, how to assess these factors, and what to do about them. The chapter on depression and heart disease does not mention the use of ECT. Most chapters that describe treatments recommend psychotropics as the treatment of choice for co-occurring depressions, whereas the chapter on chronic pain avers that ECT is the treatment of choice for melancholia. What is the primary care physician to make of that apparent conflict?

I have other problems with the book. The chapter on depression and the aged offers a relatively lengthy discussion of the psychosocial theories of comorbid depression but does not discuss suicide in this age group and, further, implies that psychological and biological treatments for comorbid depression are of equal benefit. My experience and reading of the literature suggest to me that although interpersonal and social interventions are important, biological treatment is essential in cases of major depression. The discussion of treatments of depression associated with endocrine disorders is also lacking, boiling down to the suggestion that if you treat the endocrine disorder the co-occurring depression will likely resolve. Not much meat on that bone.

It all comes down to the fundamental issue of the validity of psychiatric specialization. As a final example, the use of all sorts of psychotropic drugs is repeatedly recommended as if primary care physicians were as competent as are psychiatrists to use these agents. If they are not, then why write a book encouraging them to use these agents? If they are, why do we need psychiatrists?

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## SCHIZOPHRENIA

**International Perspectives in Schizophrenia: Biological, Social and Epidemiological Findings,** *edited by Malcolm Weller. London, John Libbey, 1990, 321 pp., $78.00.*

Malcolm Weller, editor of this volume and author of three of its chapters, opens this book with the statement, "There have been some exciting developments in the conceptualization and treatment of schizophrenia which are inaccessible without sifting a large and growing number of journals" (p. vii). Dr. Weller and his colleagues are to be congratulated. Not only does the volume they produced neatly summarize the relevant material on schizophrenia in one place, but it does so in a balanced and well-thought-out manner.

*International Perspectives in Schizophrenia* is the result of two conferences held in London in the late 1980s under the auspices of the National Schizophrenia Fellowship. Although the title includes the term "international perspectives," most of the chapters were written by British investigators. For any reader, however, the volume provides an unusually complete overview of the field.

The editor says in his preface that he wants to include information about the biology, epidemiology, and psychosocial aspects of schizophrenia. He succeeds admirably. There are separate sections on biology, genetics, epidemiology, pharmacology, and social aspects of schizophrenia. For a book as broad-based as this, the degree of sophistication of many of the chapters is a welcome surprise. A number of the sections, in fact, can be considered the definitive review of the area at the current time.

The section on biology reviews organic aspects of schizophrenia. Several of the chapters are excellent, but the review by Liddle entitled "Prefrontal and Subcortical Dysfunction in Schizophrenia" is particularly relevant to an understanding of the current theories of schizophrenic psychopathology and the potential mechanisms of action of both the typical and the atypical neuroleptic drugs.

Perhaps the strongest section in the book is the entire discussion on genetics. It provides an in-depth review of current theories and techniques. Kety reviews the well-known Danish adoption strategies, Blackwood and colleagues discuss the concept of trait markers, Ghurling and colleagues describe the use of molecular genetics techniques, and Crow presents the basis for a possible viral etiology of schizophrenia.

The section on epidemiology provides a review of techniques used in the study of schizophrenia and emphasizes in particular the need for accurate diagnostic assessment. I was particularly struck by the fascinating discussion about resource utilization in Great Britain for the treatment of schizophrenic patients. The discussion about the implications of hospital closings on social policy, a topic of great interest in the United States, is presented with a uniquely British twist.

The section devoted to pharmacology is also extremely well-done. There is a chapter by Barnes describing drug-induced akathisia and tardive dyskinesia. Jones and Costall and colleagues describe the potential value of serotonin-blocking drugs (particularly drugs affecting the $5\text{-HT}_3$ receptor) as putative treatments for schizophrenia. Van Kammen and colleagues from the United States review their thoughts on the potential role of noradrenaline as one factor involved in the response to and relapse from antipsychotic medication. Finally, Jenner and colleagues describe the drug sulpiride and its unusual $D_2$ receptor effects.

The final section, on social aspects, reviews the work of Leff on expressed emotion. It also contains a particularly interesting chapter by Falloon on family management techniques as one aspect of the overall treatment of patients with schizophrenia.

This description will undoubtedly give the reader an inkling of the diversity of the material presented in this volume. What is surprising, however, is the depth in which the authors describe their particular topics. That depth provides for the richness of the book but also may make it somewhat "rough going" for novice readers. The only addition that I would have wished to see would be more of a discussion about the role of clozapine as an atypical neuroleptic, both as a potentially more effective treatment for schizophrenia and as a probe into the neurochemical pharmacology of the antipsychotic drugs. But this is a fine point, and the volume stands on its own as it is. Any student or practitioner wishing to get a comprehensive overview of the status of research and practice relating to schizophrenia would do well to read Dr. Weller's compilation. Indeed, he and his colleagues have succeeded in putting much of the relevant information about schizophrenia in one place.

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**Office Treatment of Schizophrenia,** *edited by Mary V. Seeman, M.D., F.R.C.P.(C), and Stanley E. Greben, M.D., F.R.C.P.(C). Washington, D.C., American Psychiatric Press, 1990, 208 pp., $28.50.*

This is a concise and readable text written with the outpatient practitioner in mind. It succeeds in providing a useful overview of outpatient treatment for "the large majority of schizophrenic patients, with whom the duration of the difficulties presented by the illness can be measured not in months, but in years" (p. 3). There are 11 logically organized chapters, each a freestanding module that addresses a different aspect of treatment. Six chapters are written by the editors, and five are the product of as many other clinicians.

The first chapter explores the reluctance of many clinicians to treat these patients and makes a compelling case for undertaking long-term treatment with them. This is followed by a concise outline for conducting the initial clinical assessment. The third chapter ("Engaging Patient and Family in Treatment") seems intended for a less experienced audience, but it is well-written and reflects the work of a skilled and thoughtful clinician devoted to caring for the chronically ill.

"Individual Psychotherapy" (chapter four) provides an optimistic view of the role of individual psychotherapy in this disorder, focusing primarily on the experience of the ongoing relationship for both patient and therapist. It is very enjoyable reading despite superfluous definitions of such familiar concepts as "transference," "countertransference," "real relationship," and "working alliance." A shortcoming of this chapter is the absence of any consideration that some schizophrenic patients may not benefit from therapy and how this situation might be recognized and managed. Chapters five ("Family Therapy") and six ("Group Therapy") are clearly written and helpful to those unfamiliar with these modalities; they contain straightforward, practical information presented with a solo, office-based practitioner in mind.

In contrast, the two psychopharmacology chapters are somewhat disappointing. Chapter seven ("Antipsychotic Pharmacotherapy") contains useful observations about management issues associated with neuroleptic administration (e.g., resistance and noncompliance), but experienced practitioners will probably find it too general to be useful. Chapter eight ("Adjunct Therapies") is problematic. The stated goal of this chapter is "to outline new approaches to the diagnosis and management of some of the more common difficulties of the schizophrenic patient" (p. 143). Perhaps this explains the author's decision to highlight some unproven treatments (e.g., calcium supplementation for "neuroleptic-induced extrapyramidal reactions" and iron supplementation for akathisia) rather than focusing more on typical interventions. Individual studies are given as much weight as well-established findings rather than being presented in perspective. Sweeping statements are made without benefit of citation. Examples of these include, "Anxiety and depression are the most common symptoms of schizophrenia" (p. 143), "Currently, lithium represents the single most important and potentially useful adjunct to our conventional treatment of schizophrenia of all of the other . . . [alternative treatments] that have been proposed" (p. 152). The importance of distinguishing between depression and akinesia on the one hand and anxiety and akathisia on the other is emphasized repeatedly, but no attempt is made to provide guidelines for making these distinctions in practice. A minor point: the use of alprazolam for akathisia is discussed without ever mentioning another benzodiazepine by name.

Chapter nine ("Networking") emphasizes the importance of the psychiatrist's role as patient advocate and community liaison. Chapter ten ("Dealing With Crisis") is unfortunately too brief to adequately address the pertinent clinical crises it describes. The final chapter recapitulates the book's central emphasis on the patient-therapist relationship.

Overall, this is an enjoyable and useful book. Clinical vignettes are used generously throughout to illustrate an abundance of practical suggestions and cogent observations. It is most successful when discussing issues in the interpersonal domain and when advocating a humanistic and individualized treatment approach to this patient group. The psychopharmacology chapters appear to fall short of meeting the average practitioner's needs, however, and there is no discussion of patients with dual diagnoses or medicolegal issues. Nevertheless, anyone who treats chronic schizophrenic patients in an outpatient setting or who is contemplating doing so will find this book helpful.

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## CHILD PSYCHIATRY

**The Course of Life, revised ed., vol. III: Middle and Late Childhood,** *edited by Stanley I. Greenspan, M.D., and George H. Pollock, M.D., Ph.D. Madison, Conn., International Universities Press, 1991, 562 pp., $65.00.*

In 1980, under the aegis of NIMH, Drs. Greenspan and Pollock brought out a well-received three-volume compilation of psychoanalytic papers on normal and pathological development from birth through senescence. The present volume is the third of a greatly expanded revision of that collection, incorporating much new material and updating early contributions. It deals with the phase designated by Freud as the "latency" period—the years from about 5 to prepuberty, classified here more "atheoretically" as "middle and late childhood."

What is most notable in this multiauthored assemblage is the wide range of approaches taken by the authors, all of whom fall within the spectrum of "mainstream" psychoanalysis. Several remain wedded to "classical" libido theory, offering rather formulaic recapitulations or elaborations of the traditional literature on "latency" and thus adding little to what Anna Freud and Berta Bornstein, among others, wrote long ago. More interesting and, I believe, more clinically useful are the efforts of contributors like Marshall Schechter and Lee Combrinck-Graham and Fred Pine, who attempt to integrate psychoanalytic and cognitive approaches to development and psychopathology; Paulina Kernberg, who casts childhood psychosis in the mold of object-relations theory; and Robert Stoller, whose revisionist views of gender identity and sexual identity formation, although fairly familiar by now, are both imaginative and much in tune with current data from direct observation studies.

Other noteworthy pieces include that of Kyle Pruitt, who reports research demonstrating that fathers do very well as primary caretakers of young children, and Serge Lebovici, who offers a characteristically French approach to the assessment of psychopathology in children. Lebovici's perspective emphasizes mother-child interactions, much in the spirit of Winnicott, but he is particularly concerned with the impact of the mother's prenatal fantasies and expectations on the child's development.

As in most multiauthored collections, there is a good deal of overlap among the various essays. Reviews of the Freudian and other early literature are repeated from paper to paper in an almost ritualized form. Still, there is much of value in this anthology, not least an effort by Greenspan, Hatleberg, and Cullander to formulate a systematic approach to the assessment of early psychopathology on developmental lines—a method that may prove somewhat cumbersome for the busy clinician but would seem to be of great value for the investigator.

*The Course of Life, revised ed., vol. III* is not a book to be read from cover to cover, but it is a valuable reference source for students and practitioners who wish either to review basic psychoanalytic developmental concepts on the "latency" period or to be brought up-to-date on contemporary viewpoints within the psychoanalytic frame of reference.

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## Application of Basic Neuroscience to Child Psychiatry, *edited by Stephen I. Deutsch, Abraham Weizman, and Ronit Weizman. New York, Raven Press, 1990, 400 pp., $49.50.*

The last two decades have seen an unprecedented evolution in child psychiatry. The development of criteria-based diagnostic categories and the use of structured interviews, rating scales, and psychopharmacological interventions have all added to its developing a firmer, broader scientific basis. Nevertheless, an understanding of the neurobiological basis of childhood psychiatric disturbances remains a stepchild of these advances and a distant relative of those seen in adult psychiatry. It is within this context that I approached this book, in the hope that it would answer a number of questions concerning how neuroscience might approach childhood psychiatric disturbances and what future neurobiological investigations may hold for child and adolescent psychiatry.

The book is divided into three sections: Basic Neuroscience Considerations, Application to Specific Clinical Disorders, and Evaluation, Drug Development, and Ethical Considerations. Section one has several chapters of excellent quality that cover basic neuroscience areas and then provide either theoretical or applied links to child psychiatry. Other chapters fail to provide descriptions of future implications or demonstrations of current applications of neuroscience techniques to child psychiatry. A number of important areas that would appear to have potential applications to child psychiatry research are not covered or covered only very briefly. These include imaging techniques, endocrine challenges, brain immune interactions, and receptor strategies. Despite the authors' efforts to present coherent and broad reviews of the field of neuroscience as it applies to child psychiatry, the book does not adequately achieve this goal. Unfortunately, this accurately reflects the lack of knowledge in this area.

The second section represents the strength of the book. Here are reviews of neuroscience studies as they relate to major childhood psychiatric disturbances, including autism, pervasive developmental disorders, childhood-onset schizophrenia, Tourette's syndrome, obsessive-compulsive disorders, suicide, and Down's syndrome. In general, each one of the chapters is well-prepared. Surprisingly, no mention is made of biological studies of childhood major depressive disorders, an area that has led in the application of neuroendocrine and sleep strategies. Further, the schizophrenia chapter could have been complemented by current adult work to allow a better perspective for future research.

Section three includes a chapter on ethical issues in research in child psychiatry that is one of the book's major contributions. Some of the most important difficulties in performing research in child psychiatry are explored in this chapter.

This text represents a step in the evolution of the application of neuroscience techniques to child psychiatry. Despite its limitations, it is the only text in its class for those interested in developing an overview of major childhood psychiatric disorders and neuroscience-based studies. The book's principal shortcoming is in its effort to strive beyond application without clear links to future studies. We strongly recommend this text to those interested in research in child psychiatry and to those clinicians who are still skeptical of the potential for the application of neuroscience to the understanding of the etiology of childhood psychiatric disturbances.

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## Adolescent Psychotherapy, *edited by Marcia Slomowitz, M.D. Washington, D.C., American Psychiatric Press, 1991, 199 pp., $29.95.*

Any book covering the topic of adolescent psychotherapy is a difficult undertaking. One has only to remember that the patients are emerging from dependent childhood and are supposed to emerge as independent adults during the next approximately seven years. Innumerable physical and emotional changes take place during this period. The adolescent is struggling with many physical changes and emotional variations and is concerned about his or her own stability. Referral to a mental health worker is often met with resistance because it implies to teenagers that somebody thinks they are crazy; they are concerned that this may be true.

The authors have chosen to divide this book into three sections, Theory, Treatment, and Specific Disorders and Their Treatment. Each section has several chapters. The first chapter, which has a psychoanalytic orientation, does a creditable job in covering different psychoanalytic contributions to adolescence. The author points out a couple of things that are of tremendous importance. First, the teenage years can be divided into early, middle, and late, each having its own particular tasks. Second, the success or lack of it in terms of how well adolescence is accomplished depends in large measure on the success of the preadolescent development. A pubescent youngster who has had many problems before adolescence will bring these to the teenage years and have additional difficulty. The child who reaches adolescence successfully, however, will probably do well during adolescence.

Chapter three, "Biological Facets of Psychotherapy," is brief but touches on the most salient features of the biological development of the adolescent. The chapter entitled "Social Systems Contributions to Psychotherapy" quite correctly points out that effective psychotherapy with the teenager requires attention to both the intrapsychic and the systems variables that patients experience emotionally in social functioning. Like children, adolescents rarely refer themselves to a therapist but, rather, are sent by a responsible adult, usually a parent. This means that from the very beginning the role of each of the adults as well as the teenager must be worked out to the satisfaction of all. Adolescents are due the respect of confidentiality, and it is essential that this be given them. By the same token, the adolescent must know that the responsible adults must be brought in for consultation if something serious arises. In other words, each of the parties must understand his or her particular role in general and be willing to accept it before therapy begins.

Chapter six, entitled "Group Psychotherapy of Adolescents," points out that group psychotherapy is often essential and that many adolescents prefer it. It is necessary, however, that the group leader not become authoritarian or dictatorial. The last chapter, "Psychotherapy of Adolescents With Attention-Deficit Disorder," reminds us that one of the most common misconceptions about attention deficit disorder is that children outgrow it as they enter adolescence. This is by no means true, although it is possible that they outgrow attention deficit disorder with hyperactivity. The following three chapters discuss psychotherapy of adolescents with behavior disorders, adolescents with mood disorders, and adolescents with neurotic disorders. Each of these is concisely written and of practical value.

This book is written for all mental health workers and includes a large number of references for those who wish to pursue particular points. It is to be recommended for anyone who deals with the mental health of adolescents.

STUART M. FINCH, M.D.
*Green Valley, Ariz.*

**Adolescent Psychiatry: Developmental and Clinical Studies, vol. 17. Annals of the American Society for Adolescent Psychiatry,** *edited by Sherman C. Feinstein, Aaron H. Esman, John G. Looney, George H. Orvin, John L. Schimel, Allan Z. Schwartzberg, Arthur D. Sorosky, and Max Sugar. Chicago, University of Chicago Press, 1990, 544 pp., $40.00.*

This volume of *Adolescent Psychiatry* is a diverse collection of essays, literature reviews, and clinical research studies. It includes specific psychotherapy techniques useful in the treatment of adolescents, current theoretical concepts in development, clinical vignettes in different treatment settings, and a discussion of the impact of the current political and social climate on our work in adolescent psychiatry.

The text is divided into four sections. The first, Adolescence: General Considerations, starts with chapters by two authors who question the current "goals" of the health care system and the educational system. Frank T. Rafferty argues that in the United States the free-market economic forces of supply and demand force the health care system to operate on at least two tiers and that the "planned, controlled social engineering that would be required to truly meet all the needs of children and adolescents" is inconsistent with our culture. Richard A. Gardner provides a provocative diatribe on the failing educational system and its deleterious effects on the psychological development of children and adolescents. I found the last two chapters in this section particularly helpful for my own work with adolescents. Philip Katz discusses techniques for engaging an adolescent during the first few minutes of the first interview. His clinical vignettes clearly illustrate his points. Derek Miller concisely describes the meaning of treatment termination for adolescents in different developmental stages as well as for the hospitalized adolescent.

The second section, The Chestnut Lodge Adolescent Experience, is the weakest section in this volume. There are some highlights here, however. E. James Anthony provides a literary description of the long-term setting, describing the ideal development of an adolescent during his or her stay at Chestnut Lodge. I found Douglas A. Chavis' case study of a boy with a severe narcissistic personality disorder richly descriptive and thoughtful. His discussion of transference and countertransference should be read by any health care provider working with adolescents. The chapters on family therapy and group therapy were disappointing. Perhaps the disorganization and use of confusing jargon is proportional to the number of authors of this chapter. The chapters on the research experience at Chestnut Lodge are varied, including such subjects as personality and demographic differences in adjustment to the milieu, the attachment process in brain-damaged adolescents, and effects of the sex and experience of the therapist on psychotherapy, but most of the studies are superficially constructed. Wells Goodrich provides a well-organized overview of characteristics of adolescents who are hospitalized, the hospital treatment processes in three phases, and the four patterns of response to treatment during hospitalization. He does not pretend that the research he presents is rigorous but does provide us with questions to be studied with more reliability. Linda Beth Berman and Wells Goodrich thoroughly review the literature on runaways from home and hospital and describe a retrospective study on runaways from Chestnut Lodge. Their results must be carefully studied for clinical relevance.

The third section, Developmental Issues in Adolescent Psychiatry, is the most challenging to read but also the most rewarding. Joseph Palombo studies normal development during late adolescence within the framework of self psychology. He carefully reviews Kohut's definitions of "the cohesive self" and "the nuclear self." He then describes the work necessary to establish these developmental formations. Drew Westen and colleagues report their study of the developmental differences in object relations between borderline adolescents and adults. They question the current object relations construct on the basis of their findings that there are developmental differences in object relations between adults and adolescents. Despite the limits of the research, the question begs further study. Sheila Hafter Gray takes us beyond adolescence but within the context of a developmental continuum not marked by isolated phases. She describes the developmental tasks of young adulthood, notably the consolidation of a genital character structure. Bernard A. Stein and colleagues report data from a longitudinal study of the change and consistency in personality characteristics from middle to late adolescence. Max Sugar describes the different (and constant) anxieties during the phases of adolescence, not only for the adolescent but for the parent as well.

The fourth section, Psychopathology and Psychotherapy of Adolescent Emotional Disorders, comprises chapters devoted to specific disorders. Susan J. Bradley provides a rich overview of panic disorder with a detailed literature review and relevant clinical vignettes. Nancy H. Weil and Andrew M. Boxer describe their research on the treatment of adolescent mothers and their children with impaired attachments. They used conjoint psychoanalytic psychotherapy with the mothers and infants. The study is descriptive rather than quantitative. The cases presented illustrate the complexity of such treatment—the multiple dyadic relationships in the treatment room requiring close monitoring and the transference and countertransference issues in this treatment. Kevin R. Ronan and Philip C. Kendall, using cognitive-behavioral therapy, provide a detailed, almost "how-to" approach to the treatment of adolescents who lack self-control.

The overall quality of volume 17 of *Adolescent Psychiatry* is good. I recommend a selective reading, with more attention to the first and third sections. Reading this book made me more aware of the variety of study and perspectives within this work. This volume is broad in scope; it illustrates the complexity of this developing subspecialty.

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## RESEARCH METHODS

**An Introduction to Psychiatric Research,** *by Richard E. Gordon, C.H. Hursch, and Katherine K. Gordon. New York, Cambridge University Press, 1988, 288 pp., $37.50.*

This book provides a very general introduction to doing research in the broad field of applied general psychiatry. Its nontechnical approach combined with an amicable writing style and moderate level of content makes the book readable by even the least experienced. Although not stated, the intended audience is either a student who has just started training or a more advanced practitioner with very little exposure to research. The broad scope addresses subjects ranging from how and where to get an idea to rewriting rejected manuscripts. The cost of this broad coverage, however, is that few subjects are covered in depth and many topics receive only cursory examination.

The authors organized the chapters following a classification scheme that groups research efforts into six progressive categories: 1) research to develop an initial working hypothesis (literature reviews or clinical impressions backed by single sample descriptions), 2) research on scale or instrument development, 3) "observed relation research" (simple correlational studies with no causal inferences), 4) "observed causal research" (weak experimental, quasi-experimental, or correlational studies with causal inferences), 5) "causal relation research" (case-control or experimental research), and 6) theory development work (synthesizing and formalizing previous research information).

The chapters address each type of research in turn. Additionally, there are chapters on some simple statistics, research ethics, and other general introductory issues.

From my perspective as an active researcher and biostatistician who has taught research methods, I welcomed the progressive arrangement. By organizing research efforts on the basis of level of development the authors avoided a common pitfall found in many introductory texts: using a simple correlational versus experimental dichotomy for the sake of simplicity. Grossly simplifying important ideas often causes more confusion than it tries to avoid. The confusion—due to lack of fit—frequently becomes clear as soon as the system is applied to real situations.

In contrast, Gordon, Hursch, and Gordon show how the chapters relate to real research by featuring at least one or two of their own published research projects as examples for each type of research presented. These provide the reader with actual examples of research issues (e.g., postpartum reactions). These also demonstrate the progressive nature of a long-term research project and add continuity to the book. On the other hand, there are few examples of the research of others, so the examples may not represent general psychiatry. For instance, few strictly biological or physiological examples are detailed.

Unlike the clear organization of the chapters, the text within a chapter often jumps unexpectedly from one topic to another. It is sometimes difficult to see the connection between paragraphs that appear one after the other within a chapter. For instance, in chapter two the flow of topics proceeds immediately from library computer searches (e.g., MEDLINE) to descriptive statistics and the normal distribution and then to writing up a paper. Sometimes ideas that are introduced are not discussed until several pages later, and, occasionally, definitions are presented following the discussion of an item.

At times, the order in which ideas are introduced could result in perceived inconsistencies. For instance, in the chapter on developing measuring instruments, the subheading "Getting Subjects for Research" suggests that good places to obtain subjects are in the reader's (i.e., a psychiatrist's) waiting room or a hospital. Random sampling is then appropriately defined on the next page, and on the following page is a warning not to use special groups selected on the basis of convenience. These unintentional problems with continuity make the material hard to follow, but, fortunately, most occur in the early chapters; subsequent chapters flow smoothly.

Some individual topics are presented too superficially for reasonable coverage. For instance, reliability and validity receive perhaps a couple of pages of text. In this quick treatment, criterion-related validity is mentioned only in the context of concurrent validity. As another example, the book deals with scales of measurements using the classifications of S.S. Stevens (1) (nominal, ordinal, interval, and ratio). Gordon and colleagues do not cite Stevens' work but do repeat his rather dogmatic, even odd, admonitions about performing arithmetic operations on certain numbers. Stevens' warning would preclude figuring scholastic grade-point averages because these require adding and dividing by N. In practice, most people have no difficulty with the concept of calculating grade-point averages using addition and division. Calculating means from most psychiatric rating scales would also be taboo according to Stevens' rules. There is little discussion of how measurement scales relate to psychiatric research.

According to the authors, measurement scales determine whether to use parametric (e.g., t tests) versus nonparametric (e.g., Mann-Whitney U tests) statistics. Nothing is said in this context about normal versus nonnormal distributions or any other assumptions about parametric statistics. The introduction to normal curves appears in an earlier chapter with only a vague reference to subsequent statistical analysis. In practice, violating the assumptions of parametric statistics leads one to consider the nonparametric alternatives and not whether the scale of measurement is interval or ratio. It would appear that most of this book's wisdom about this issue comes from the introduction to Siegel's book (2), which is heavily influenced by Stevens' notions about doing arithmetic on numbers. However, even nonparametric statistics require some arithmetic and would thus, according to that rule, be inappropriate for many measurements of interest to psychiatrists. This oversimplified and somewhat dogmatic notion may do more harm than good.

In general, the treatment of statistical material is very traditional but usually much like a cookbook. There are no references to any of the newer graphical techniques (e.g., box plots). There are numerous worked examples of simple analyses. The instructions for calculating chi-square are unnecessarily difficult. The simple and general formula is not presented until after a couple of different calculational methods. Also when a two-by-two chi-square is first introduced with low expected frequencies (fewer than 5), Yates's correction is offered as the solution and not Fisher's exact test. Fisher's exact test is referenced later. The discussion of statistics often mentions the sound advice of seeking help from statisticians and using a personal computer.

In many ways this book is a good practical guide for beginning researchers. It is simple and specifically concerned with general psychiatric research. I had some problems with the material because introductory books by nature of their intent need to be almost pristine. An introductory book has a good chance of being the only book a person might read on a subject. Also, the reader of an introductory book may not be in a position to judge its accuracy. If this book were used for a course, supplemental material would be absolutely necessary to provide examples from other research areas. More detailed discussion of other perspectives could also be provided by including some original source materials on quasi-experimental methods.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Media Coverage Versus Fluoxetine as the Cause of Suicidal Ideation

SIR: Since the publication of an article by Martin H. Teicher, M.D., and associates (1) on six case reports of patients who experienced suicidal ideation with fluoxetine treatment, the media have paid close attention to the phenomenon. Stories concerning the fluoxetine defense for violent crime and suits brought concerning suicidal ideation have been reported. The following case reflects some of the difficulty in treating patients with fluoxetine during this time of intense media attention.

> Mr. A was a 49-year-old man who was HIV positive but asymptomatic. He was first seen psychiatrically with complaints of anxiety. On examination he showed evidence of anhedonia, feelings of guilt, depressed mood , and thoughts of death for the past 6 months. Recent losses included the death of his mother 6 months earlier. He was doing well medically but refused to take zidovudine because he heard that it had serious side effects. A regimen of fluoxetine, 20 mg every morning, was begun, and within a week the patient returned, stating that he had stopped the medication. He claimed that the medication made him feel "horrible on the inside" but he had no idea what the cause could be until he saw the news on a local channel which covered a story of a woman who had made suicide attempts and who attributed this to fluoxetine. He claimed that his symptoms began before the broadcast and that he knew they were the same. Convinced that the fluoxetine was the cause of this "horrible" feeling, he became fearful of the medication, stating that he did not want to kill himself (which by now he was convinced he would do if he continued the medication).

This case reflects some of the difficulties that the recent media coverage may cause. The patient had already shown a reluctance to take medication because of the side effects that he was told might occur. He was also unable to state what the feeling was, instead stating that it sounded like what he saw on television. It is unfortunate, given the need to document information on adverse effects of the psychotropic agents, that such confusion concerning the etiology was present.

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## Carbamazepine-Induced Atrioventricular Block

SIR: Carbamazepine is currently widely used in neurology and is now more and more recommended for lithium-resistant and rapid cycling patients. Carbamazepine-induced cardiac electrical conduction disorders have previously been reported in patients already suffering from a cardiac condition, but little is known about electrical abnormalities appearing in an otherwise normal heart.

> Ms. A, 63 years old, had been treated for a unipolar affective disorder with periods of mood-noncongruent psychotic features for the past 10 years. All previous heart evaluations, including ECGs, had been normal. She was admitted to the hospital for a depressive psychotic episode and slight signs of confusion. Neuropsychological tests suggested features of organic brain disorder. CT scan showed calcifications in basal ganglia and slight cerebellar atrophy. ECG showed bilateral temporal theta waves with irritative features. Carbamazepine, 100 mg b.i.d., was introduced and brought a progressive improvement. She was followed up for 3 years as an outpatient and showed sustained clinical stability and even improvement on neuropsychological tests.
>
> After 3 years, Ms. A presented an effort dyspnea. ECG was normal but the treadmill stress test showed a second-degree atrioventricular block, and episodes of third-degree atrioventricular block with ventricular escape were documented on Holter monitoring. No symptoms of intoxication were found. Carbamazepine was stopped and dyspnea disappeared. Because her psychiatric condition rapidly worsened, carbamazepine was reintroduced with close supervision. After a few weeks, cardiac symptoms reappeared and the drug was definitely stopped. Holter monitoring was normal thereafter, as were ECG, thallium stress test, and echocardiography. ECG never showed conduction defects on follow-up.

According to Hewetson et al. (1), Steiner, in 1970, reported that carbamazepine prolongs atrioventricular conduction time in dogs. Meyrignac et al. (2) reported cases of carbamazepine-induced complete atrioventricular blocks. Boesen et al. (3) reported on other abnormalities such as an intermittent complete atrioventricular block, an atrioventricular block with a functional escape rhythm, and an intermittent asystolia. Others like Benassi et al. (4) and Ladefoged and Mogelvang (5) have reported carbamazepine-induced heart conduction disorders, but in patients with already-known heart disease.

Our patient seems to be a rare case of a pure carbamazepine-induced severe heart conduction disorder without previous heart disease. It is interesting also to note that symptoms appeared 3 years after the beginning of the drug treatment without apparent preceding symptoms. The most plausible physiopathogenic explanation for this phenomenon is the chemical structure of carbamazepine (like tricyclics), with quinidine-like effects on cardiac conduction pathways.

We therefore recommend that dyspnea, dizziness, or syncope appearing in a carbamazepine-treated patient should be taken seriously, even in the absence of other cardiac symptoms and an apparently normal heart. ECG is not necessarily adequate to detect conduction defects, and it therefore should be complemented by a stress test and Holter monitoring if ECG is not demonstrative. If carbamazepine is the only drug to which such a patient responds, a cardiac pacemaker should then be mandatory.

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## Successful Treatment of Bowel Obsessions With Nortriptyline

SIR: Several authors have described individuals who suffer from agoraphobia without panic, or from social phobia, whose incapacity rests in an excessive preoccupation with the sudden loss of bowel control (1, *DSM-III-R*). Some have called these worries "bowel obsessions" and have suggested that the condition is a variant of obsessive-compulsive disorder (2–4). Case reports have documented successful treatment with clomipramine, doxepin, imipramine, and behavioral techniques (2–4). I am reporting the case of a patient whose symptoms responded to nortriptyline.

> Mr. A was a 65-year-old man who presented preoccupied with the worry that he would be flatulent in public. He had never been flatulent around other people. The problem had developed 30 years earlier and had progressed with negligible waxing and waning in its course. It was followed by extreme social withdrawal and the loss of a very successful business career. Prior treatment with psychodynamic psychotherapy, diazepam, chlordiazepoxide, propranolol, and dicyclomine had produced no improvement. Treatment with adinazolam had produced a modest benefit but had to be stopped because of impotence. Trials of fluoxetine, alprazolam, and clomipramine produced no benefit. After 3 weeks on a regimen of nortriptyline, 10 mg/day, he noticed a "remarkable improvement" never before felt in his life. He was much more comfortable in public, much less preoccupied with being flatulent, and able to triple his activities. At a dose of 50 mg at bedtime there was further improvement. The blood level at this dose was 167 ng/dl. These beneficial effects continued unabated after 6 months.

This patient's case and the literature discussed raise the question of how to classify bowel obsessions. The presence of recurrent, intrusive, senseless thoughts suggest that this is a variant of obsessive-compulsive disorder. In Mr. A's case, the lack of success with two serotonin uptake blockers argues against this hypothesis. The type of incapacity seen in the condition argues in favor of it being a social phobia. Response to several different treatments, particularly benzodiazepines, suggests that anxiety reduction is a factor in improvement. Although this is an uncommon problem, the disability to which it leads is profound, and the relief after treatment is greatly appreciated. It is hoped that future study will shed more light on the classification and treatment of this interesting disorder.

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## Treatment of Generalized Anxiety Disorder and Trichotillomania With Buspirone

SIR: To my knowledge there has been no previous report to document the use of buspirone in the treatment of an anxiety disorder with coexistent trichotillomania.

> Ms. A, a 31-year-old woman, presented with several months of paroxysmal episodes of acute anxiety accompanied by attendant autonomic hyperactivity. This included the occurrence of hyperventilation, palpitations, dyspnea, and paresthesias. The patient also exhibited an uncontrollable urge to pull out her hair. This occurred over the same period of time and resulted in a section of alopecia.
>
> She reported intrusive thoughts of having an underlying disease state, despite reassurances from physicians on several occasions. This state did not appear to meet the criteria for obsessive-compulsive disorder.
>
> A previous 2-week trial of alprazolam appeared to be of no benefit. Ms. A was then started on a regimen of buspirone, 30 mg/day p.o. Within 4 weeks, the trichotillomania remitted completely. A significant improvement of anxiety symptoms was noted on the Sheehan Patient Rated Anxiety Scales.

Previous studies have documented successful treatment of both obsessive-compulsive disorder and trichotillomania with clomipramine, a strongly serotonergic tricyclic antidepressant (1, 2). Buspirone, a well-known anxiolytic agent, a 5-hydroxytryptamine agonist, is also thought to affect serotonin balance. This agent was shown to facilitate the effects of fluoxetine in the treatment of obsessive-compulsive disorder (3). These studies may offer an explanation of the efficacy of buspirone in this case.

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## Lithium Treatment of a Bipolar Patient With Cystic Fibrosis

SIR: We are reporting the case of a patient with cystic fibrosis and bipolar disorder who was treated with lithium. This case is of interest because of a hypothesis suggesting that lithium may correct the defect in chloride transport seen in cystic fibrosis (1).

> Ms. A was a 30-year-old woman with cystic fibrosis who had had episodes of mania and depression of increasing frequency and severity since she was 19 years old. She was first hospitalized 2 years ago when she was acutely psychotic with mixed depressed and manic symptoms. She was successfully treated with lithium carbonate and chlorpromazine, and she was discharged on lithium maintenance. After 6 months she was readmitted with mania and psychosis. She responded well to lithium carbonate and perphenazine, but this hospitalization was complicated by pneumonia. She continued to do well on these medications 6 months after discharge.
>
> Serial electrolyte determinations from serum and sweat were made initially and after 2, 3, 5, 7, and 8 months. Ms. A's serum lithium levels were 0.97, 0.87, 0.93, 0.90, 1.24, and 1.02 meq/liter, respectively, at a consistent dose of lithium carbonate, 450 mg b.i.d. Measured simultaneously in sweat, lithium levels were <0.1, 1.8, 1.6, 2.08, 2.36, and 3.2 meq/liter, and chloride levels were 102, 93, 126, 88, 128, and 121 meq/liter.

Cystic fibrosis is an autosomal recessive disorder of defective chloride transport in the epithelia of organs of exocrine function caused by a mutation on chromosome 7 (2). The defect in chloride transport in cystic fibrosis may be influenced by lithium. Calcium functions as an intracellular second messenger in many cellular processes, and lithium can counterbalance the effects of calcium abnormalities, as suggested in lithium treatment of bipolar disorder (3). There is some controversial evidence that the intracellular pool of calcium is increased in cystic fibrosis cells, which led to the hypothesis that lithium might limit the amount of intracellular calcium and restore normal membrane permeability to chloride (1). Clinical trials of 10 weeks of lithium therapy for patients with cystic fibrosis caused a decrease in sweat chloride in two-thirds of the subjects but also a mild reversible decline in pulmonary function (4). There has been one other young woman with manic-depressive disorder and cystic fibrosis treated effectively with lithium (4).

Lithium therapy for our patient had no apparent impact on cystic fibrosis, but it was beneficial for mood disorder. Her response to lithium therapy and her lithium levels in serum and sweat were similar to those of other patients with bipolar illness without cystic fibrosis. An initial decrease in sweat chloride was reversed in later determinations, which calls into question the hypothesis that lithium can reverse the underlying defect in cystic fibrosis by its influence on intracellular calcium.

With regular determination of serum lithium levels and monitoring of renal and pulmonary function, lithium therapy appears to be an effective option for treating mood disorders in patients with cystic fibrosis.

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## Massive Ingestion of Trihexyphenidyl

SIR: The abuse of trihexyphenidyl and other anticholinergics for euphoric or psychedelic effects has been previously documented (1–5). The following case report serves as a reminder that some individuals may take larger than prescribed doses to diminish depression and improve functioning (1, 3–5). The case is particularly notable because of the unusually large doses of trihexyphenidyl that were ingested.

> Ms. A, a 33-year-old mother, was brought to the emergency room by her family because of restlessness, depression, and periods of confusion. She had dry skin, dry mouth, and blurred vision and showed disorientation for time. Auditory hallucinations, which had been sporadic for 2 or 3 years, intensified, and visual hallucinations began 2 weeks prior to her presentation. She was transferred to a psychiatric inpatient unit.
>
> Two weeks prior to presenting to the emergency room, Ms. A had separated from her husband because of marital discord. For the past 8 years she had been treated with trihexyphenidyl, 5 mg t.i.d., for a longstanding neurological disorder characterized by spasticity and deformity. She admitted to chronic abuse of her medication which had exacerbated during the past 2 weeks. During this period, she took approximately nine tablets (45 mg) daily, sometimes ingesting this amount in a single dose. Six months previously, after a period of increasing abuse, she had, on several occasions, ingested as many as 21 tablets (105 mg) over a time span of a few hours. She stated that during that period, marital stress and the loss of a homemaker overwhelmed her. She felt that the large doses of medication had improved her mood and level of activity. She used devious means to obtain trihexyphenidyl and knew she was "hooked" on it. There was no recent use of any other drugs and no previous psychiatric hospitalization.
>
> During her hospitalization the only medication used was lorazepam, as needed. Visual hallucinations cleared rapidly, disorientation soon after, and depression and auditory hallucinations in a few days. No substantial withdrawal symptoms were noted. Her longstanding neurological condition was diagnosed by a consultant as cerebral palsy. The psy-

chiatric impression was adjustment disorder with depressed mood and anticholinergic psychosis (hallucinosis).

While doses of 45 mg/day of trihexyphenidyl would not be unusual in a patient who abuses or is dependent on this medication (1–5), we have not seen reports of individuals ingesting daily doses of 100 mg or more. Rubinstein's estimate that a patient in a particular month "had probably received at least 2000 mg" of trihexyphenidyl (2) stands out in the literature as the largest amount presumably abused by a patient, but there is no statement as to his actual daily dose.

The fact that Ms. A did not suffer severe toxic effects from her massive ingestion 6 months previously may have been attributable to the development of tolerance reported with antimuscarinic agents (5). Her current decompensation on lower doses of trihexyphenidyl may have been due to a more rapid acceleration of dosage permitting less time for tolerance, along with the psychological effects of the breakup of her marriage.

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## Spouses' Assessments of Alzheimer Patients' Response to THA and Lecithin

Sir: Following a recent report by Summers et al. (1) of dramatic improvements in Alzheimer patients treated with tetrahydroaminoacridine (THA, or tacrine), there has been some controversy in the various media about the magnitude of this drug's clinical benefits. Despite the study's methodological problems (2, 3), reports by family members that THA caused significant improvement have been widely published.

We recently reported results of our clinical trial of oral THA and lecithin (4). We have also evaluated spouse perception of patient performance during that double-blind trial. In addition to standard investigator assessments, five of the 10 original inpatients were blindly evaluated for behavioral and cognitive improvement by their spouses. At the end of each of 3 weeks, the same nurse and the spouses, each of whom was previously trained to administer the Nurse's Observation Scale for Inpatients (NOSIE), independently rated the patients' behavior. Due to significant liver enzyme abnormalities in four patients, only six of the 10 inpatients were able to continue in a subsequent 15-week double-blind outpatient phase. In addition to investigator measures of behavior and cognition, all six spouses completed weekly the Geriatric Evaluation by Relatives Research Instrument (GERRI), an outpatient measure of cognition, mood, and social behavior.

Inpatient phase analysis of variance revealed that THA had no significant effect on spouse perception of patient performance on any of the five NOSIE scales. Correlation between spouse and nurse perceptions was low (r=0.18). During the outpatient phase, only one of six spouse ratings (GERRI cognitive scale) agreed with investigators' positive cognitive ratings, whereas two of six spouse ratings agreed with investigator assessments which found no cognitive change between drug and nondrug periods. Investigators' measures revealed some cognitive improvement in three outpatients. Only one spouse was able to distinguish correctly the THA period from placebo. This subject improved markedly on the GERRI mood and social scales but not the cognitive scale. Furthermore, there was no significant improvement in spouse-assessed functional capacity of patients, although spouses frequently expressed the belief that THA was able to improve the cognitive performance of the patients.

Our results suggest that improvement under THA, as measured by the investigators, was modest, restricted essentially to cognitive measures, and limited to a fraction of the patients (4). These findings appear largely undetected in the blinded spouse ratings. However, informal spouse impressions consistently praised the effects of the drug. Poststudy pressure to provide THA was high despite minimal findings. We believe that spouses' desire to see hope in new treatments for this disease renders objectivity regarding these treatments difficult.

Whereas a small number of Alzheimer patients might benefit modestly from THA, neither dramatic improvement nor low toxicity has been substantiated thus far. This suggests that THA must be thoroughly evaluated, including its ability to promote actual functional gain beyond test score improvement without undue toxicity for aged patients. If marketing and monitoring of THA become greater possibilities, questions of cost versus risk to the elderly should be discussed in an open debate involving the public and diverse representatives of the medical community as well as private interests. Premature closure on such a debate could adversely affect those who can least afford to pay or risk adverse effects for marginal gains.

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## Prevalence of Depressive Symptoms Among White and African-American Caregivers of Demented Patients

Sir: Dementia is characterized by a slow, progressive process that includes both cognitive and functional deterioration as well as a variety of behavioral disturbances (1). The occurrence of dementia affects family members in many ways, including increased risk for mental health problems such as symptoms of depression (1). Studies have shown that about

50% of caregivers suffer from symptoms of depression (1). While a number of variables affecting depression among caregivers have been investigated, relatively little is known about the prevalence of depressive symptoms among caregivers from different ethnic groups living in the United States. The lack of data on African-American demented patients and their caregivers is of particular concern, since this population, especially its older members, has been increasing dramatically in recent years (2).

Presented here are the preliminary findings from baseline evaluation of a cross-cultural prospective study to assess the mental health of white and African-American caregivers of demented patients in South Carolina. Eighty-three patients and their caregivers (63 white non-Hispanics and 20 African-Americans) were randomly selected for interview from the more than 5,000 demented patients currently identified in the State of South Carolina Dementia Registry and area support groups. The mean age for patients was 76.9 years and for caregivers was 61.1 years. There were no statistically significant differences in patient or caregiver age among the two groups. There were no significant differences in socioeconomic status and educational background between the two groups of caregivers. There were also no significant differences between the two groups in the sex of patients or caregivers. The sex distribution among patients was roughly equally distributed among males and females, while the caregivers were primarily females. Fifty percent of the patients in each group were considered mildly or moderately impaired, with the remaining 50% considered severely impaired according to the Global Deterioration Scale.

Symptoms of depression among caregivers were studied using the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (3). The results of this preliminary survey show significant differences in the prevalence of depressive symptoms among the two groups. African-American caregivers demonstrated significantly less depression than white caregivers when the data were analyzed using a cutoff value of 16 to differentiate among those who presented significant levels of depression. Using this cutoff our sample showed that 62% of the white caregivers had significant symptoms of depression, while only 30% of the African-American caregivers exhibited symptoms of depression ($p<0.05$). When a lower cutoff of 9 was utilized, significant values were also present, with 78% of the white caregivers, compared to only 41% of the African-American caregivers, presenting with comparable levels of depressive symptoms ($p<0.05$). Similar patterns were found when CES-D Scale mean scores were compared (for white, mean=19.3; for African-American, mean =12.4; $p<0.05$).

These findings are consistent with previous publications reporting increased levels of depression among caregivers of demented patients (1, 4). These findings support earlier data reported by Mintzer et al. (4), who found significant differences in caregiving patterns between Hispanic and matched white caregivers. The preliminary findings reported here tend to confirm the existence of ethnically bound differences in the prevalence of mental health symptoms, especially depression, among caregivers of different ethnic groups. These findings highlight the need for increased research efforts in this area and further exploration of the interaction between culture and mental health in elderly patients.

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## Diagnostic Criteria for Multiple Personality Disorder

SIR: If multiple personality disorder occurs in as many as 5% of psychiatric inpatients (1), but most psychiatrists, guided by *DSM-III-R*, diagnose it rarely, then the current diagnostic criteria clearly have inadequate sensitivity. To improve not only sensitivity but also validity, I propose the following revision of the diagnostic criteria:

The existence within the person of two or more distinct personalities or personality states (each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self) that recurrently control the person's behavior and result in an inability to recall important personal information that is too extensive to be explained by ordinary forgetfulness. The personalities often present as a puzzling changeability or incongruity of the person; their amnesia usually must be inquired for; and they must satisfy certain requirements, as follows.

A. Puzzling changeability or incongruity as indicated by one or more of the following:
   1. Kaleidoscopic presentation: The person has received a succession of different diagnoses or is diagnostically controversial because of a polysymptomatic, changeable presentation.
   2. First-rank symptoms in a person who is not basically psychotic. For example, a person hears voices conversing in his head, but does not have loose associations, flat affect, poor reality testing, poor interpersonal relatedness, mania, psychotic depression, or other medical conditions to account for the voices. (In multiple personality disorder, first-rank symptoms may be the presenting personality's experience of other personalities' acting from behind the scenes.)
   3. States: A person who is usually alert, mature, and oriented has recurrent episodes of altered states of consciousness, childlike behavior or disorientation that cannot be accounted for by intoxication, epilepsy, dementia, or other medical conditions.
   4. Changeable personal attributes: recurrent puzzling changes in knowledge, skills, tastes, values, attitudes, visual acuity, allergic responses, or other personal attributes.

B. Amnesia for extensive, complex, nonautomatic behavior (not due to intoxication, epilepsy, or other medical condition) as indicated by a positive answer to any of the following questions:
   1. Do people say that you do things that you honestly don't remember doing?
   2. Do you ever find that things have been done or changed, and nobody else could have done it, but you don't remember doing it?

3. Do you ever find yourself in places but can not recall how you got there?
4. Do you ever have difficulty remembering where you were and what you were doing during the preceding hour?
5. Are there years or areas of your life for which you have much less memory than you would expect to have?

C. Alternate personalities, which must have 1) their own independent sense of personhood, 2) their own memory bank, and 3) a history of recurrently controlling the person's behavior since childhood, or at least prior to any legal problem or psychiatric evaluation.

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## Body Dysmorphic Disorder: A Controlled Study of Patients Requesting Cosmetic Rhinoplasty

SIR: In the recent article by Katharine A. Phillips, M.D. (1), she noted a lack of controlled studies of patients undergoing cosmetic procedures. I would like to report a sample (unpublished 1980 thesis) of 20 patients drawn from a waiting list for cosmetic rhinoplasty who were compared to a control group on measures of psychiatric morbidity and body image tests. Both groups were administered structured psychiatric interviews and psychological self-report measures. The patients were significantly more disturbed on measures of psychiatric morbidity than the control subjects and scored higher on measures of neuroticism and social anxiety and lower on measures of extroversion. Most patients were rated as having moderate to severe personality disorders (Schneiderian sensitive and insecure types). No patients were psychotic.

A second group of tests concerning body image perception were also administered. These included subjective and objective measures of degree of deformity as well as specific tests of perception of nose size, utilizing both drawing and visual magnification techniques. Objective observer ratings of deformity for both groups were similar and within the minimal to mild range, although patients saw themselves as significantly worse than did control subjects. Thus, the patient group arguably fulfilled one of the essential criteria for *DSM-III-R* body dysmorphic disorder: the preoccupation with some imagined defect in appearance in a normal-appearing person, or one with a slight physical abnormality, where the concern is grossly excessive.

The main hypothesis of the study was that the experimental patients would have a less accurate perception of their nose size than the control group. The main finding was that the experimental group in fact had a more accurate perception of nose size according to two independent measures of nose size estimation. Furthermore, from the small number of postsurgery assessments following the same protocol, there was evidence that after surgery, patients' estimation of nose size became less accurate and fell within the range of the normal control subjects.

The role of cosmetic surgery in altering body image perception in these patients remains controversial, although clearly a number of uncontrolled studies do indicate significant positive changes, at least in the short term. Some recent studies of behavioral desensitization (2, 3) to dysmorphic symptoms suggest the possibility of a cognitive-behaviorial approach for some patients with this disorder. One plausible explanation in the case of cosmetic surgery would be that these sensitive personalities cognitively overfocus on the dimensions and shape of their noses, in comparison to normal persons, by spending excessive amounts of time looking at themselves in mirrors. This was reported by all patients in this study and is quite different from the mirror avoidance behavior of anorexic patients. Intuitively, this would give some basis for their more accurate perception of organ size in comparison to the control subjects. After surgery, the nose is heavily bandaged for a number of weeks; therefore this "overscanning" of the nose is no longer possible. These findings are also compatible with cognitive overfocusing as an aspect of an obsessive-compulsive disorder, one component of which is the compulsive examination of the nose and associated obsessive ruminations about it, with the accompanying increase in accuracy of nose size perception found in the experimental group. Further exploration of these body-size estimation techniques may be of value in defining more effective treatment approaches for these patients.

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## Dr. Phillips Replies

SIR: Dr. Jerome's study is interesting and adds to the literature on body image perception and psychological and psychiatric assessment in cosmetic surgery patients. However, as is the case with most studies of cosmetic surgery patients, it is difficult to determine whether his findings apply to body dysmorphic disorder, as it is not clear that the patients described had this specific disorder. Although many patients with body dysmorphic disorder seek and obtain cosmetic surgery, it cannot be assumed that all patients seeking cosmetic surgery have body dysmorphic disorder. Presumably, most cosmetic surgery patients simply want to improve their appearance and do not necessarily have an intense, distressing, time-consuming, pervasive, and impairing preoccupation with an imagined physical defect.

This issue highlights the need for diagnostic instruments and more specific diagnostic criteria to aid in the diagnosis of body dysmorphic disorder. The addition of a new criterion to this disorder's proposed *DSM-IV* definition should be useful in this regard; this criterion specifies that to meet criteria for body dysmorphic disorder the preoccupation with the imagined physical defect must cause marked distress or significant impairment in social or occupational functioning (1). It is hoped that this criterion will help differentiate body dysmorphic disorder patients from individuals with "normal" concern over appearance and from those who seek cosmetic surgery but do not have body dysmorphic disorder.

I would also add that although Dr. Jerome mentions the potential benefits of cosmetic surgery in body dysmorphic disorder, much of the literature (2,3) and my and my colleagues' work (4) suggest that surgery is generally not helpful to these patients over the longer term; they often develop more intense or new preoccupations and may have repetitive, unsuccessful surgical procedures in their disappointing search for a physical solution to a psychiatric problem.

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KATHARINE A. PHILLIPS, M.D.
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## Long-Term Effects of Incest

SIR: We read with great interest the article by George R. Brown, M.D., and Bradley Anderson, M.D. (1) about psychiatric morbidity in patients with abuse experiences. We have also carried out research on the prevalence and the consequences of incest in patients with mental disorders and in more than 1,000 male and female nonpatients. We think that our findings (2, 3) confirm and supplement Dr. Brown and Dr. Anderson's results. Like other investigators (4–6), we found various psychopathological conditions and no definite, dominating clinical picture, no typical "incest syndrome." However, self-injurious behavior, anxiety symptoms, and forced sexual behavior proved to be the main symptoms of sexually abused patients.

Some differences can be determined in family risk variables between the sexually abused psychiatric patients and the nonclinical sample with experience of sexual abuse in childhood. Multiple impulsive personality disorder and alcohol abuse in fathers and depression in mothers could be found in the first group. Mothers of sexually abused psychiatric patients were often not accepted as confidantes or protectresses because of their own emotional and social deficits or disturbance, and thus were not experienced as supportive. The familial situations of the nonclinical sample were frequently characterized by financial problems, by a mother with a physical illness or drug abuse, and by an impulsive or helpless father.

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## Dr. Brown Replies

SIR: The work of Dr. Kinzl and Dr. Biebl, published subsequently to ours, indeed supports some of our conclusions, especially with respect to the central role of suicidality in adults with abuse histories. The distinction between a "patient" and a "nonpatient" is often tenuous and associated with economic issues and other factors influencing access to psychiatric care in the United States. Therefore, we are not surprised to see confirmatory findings in the European studies by Dr. Kinzl and Dr. Biebl. Their work, studying women referred to a psychosomatic clinic, found high rates of somatoform disorders (33% of 33 abused women) and sexual dysfunction (90%), which was not supported by our work with unselected, consecutively admitted inpatients.

The notion of an "incest syndrome" is compelling but largely unsupported by empirical research with our large group of inpatients and, now, with a comparably sized nonclinical sample in the work of Drs. Kinzl and Biebl.

The role of alcohol use disorders in fathers appears to be pivotal in the family histories of adults abused as children irrespective of the source of the study population. We believe the primary and secondary prevention aspects of this finding are critical.

Dr. Kinzl and Dr. Biebl speculate on the etiology of maternal contributions to the abusive environment. This remains an understudied phenomenon, complicated by the beliefs of some clinicians that abusive families are composed of an "offending parent" (father or stepfather) and a "nonoffending parent" (mother). For example, while serving on the U.S. Air Force Task Force on Child Sexual Abuse, I learned that this terminology was in widespread use by mental health care professionals assigned the duties of case finding, evaluation, and treatment of child abuse in the military environment. The extent to which mothers are aware of abuse perpetrated by others and fail to acknowledge this or intervene on behalf of the abused child may itself be an independent factor in the expression of adult psychopathology.

Although Drs. Kinzl and Biebl report that they have studied both male and female students, their published work to date has focused on findings in women. We look forward to their future analyses that may help to address the virtual absence of information regarding the contributions of abuse to adult male psychopathology (i.e., boys and men as victims).

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## Dissociation and Suicide in the Young

SIR: Herbert Hendin, M.D. (1) has stressed the important theme that attention to the psychodynamics of suicidal patients is essential for proper therapy. Given this, it is curious that he did not mention it in multiple personality disorder, the group of patients with perhaps the highest suicide attempt rate of all mental disorders. Ross (2) found 72% had made suicide attempts. Their common psychodynamics help in understanding not only their suicidal behavior but also posttraumatic stress disorder (PTSD), conditions which manifest a high degree of dissociative experiences (3) and symptoms (4). Dissociation was the primary psychodynamic in the suicide attempt of a 37-year-old American Vietnam veteran with symptoms of PTSD (5). Dissociation phenomena do not appear to be included in the author's considerations of cognition and meaning of suicide and psychodynamics. Does the author consider dissociation in his overall scheme of psychodynamics of suicide attempts, or does he reject it and regard it as irrelevant?

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## Dr. Hendin Replies

Sɪʀ: Although there is some evidence suggesting that suicide attempts may be associated with dissociative disorders, there is to date no evidence that dissociative disorders are associated with a high incidence of actual suicide. There is therefore no reason as yet to regard patients with dissociative disorders as being at high risk for suicide.

There is evidence that PTSD is associated with suicide attempts, but dissociative experiences have not been found to be the major predictive factor of suicide attempts in Vietnam veterans with PTSD. In our study of 100 veterans with PTSD, 20% had reliving experiences that could have led to their being diagnosed as having a dissociative disorder. Suicide attempts were not a significant factor in this group (1, 2).

The case in the literature referred to by Dr. Jensen concerns dissociative experiences in a Vietnam war veteran suffering from schizophrenia and PTSD. Since patients with both disorders are at higher risk to make a suicide attempt, one can not conclude too much from such a case. The case does underline the need to look beyond a diagnosis for an explanation of suicide, since a majority of patients with diagnoses that have a high risk for suicide, such as depression, alcoholism, and schizophrenia, do not kill themselves.

A psychodynamic formulation of the case cited would need to account for the patient's delusions that a conspiracy existed to prove him homosexual, for his belief that odors emanating from his hemorrhoids repelled women, and for the fact that after a fight with his parents he shot himself when being pursued by the police while walking with a shotgun toward the home of a girlfriend. His dissociative episodes appear to have been an important part of the defensive system he erected to protect himself against his conflicts.

Splitting as a defense, of which dissociation is an extreme form, is important in suicidal patients, since one part of the self is often being attacked by another. The psychodynamics of suicide include an understanding of why such an attack is necessary and why, for some, death is the only acceptable resolution.

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## Depression After the Death of a Spouse

Sɪʀ: Sidney Zisook, M.D., and Stephen R. Schuchter, M.D. (1) studied men and women whose spouses had recently died and described the frequency of depressive syndromes during the first 3 months thereafter. I will criticize a few of the less central statements made in this fine, welcome, and lucidly described study. First, I remind readers that of the 350 spousally bereaved subjects, 24% met the *DSM-III-R* criteria for depressive episodes 2 months after the death, 23% at 7 months after the death, and 16% at 13 months after the death, in comparison to 4% of a comparison group. My comments concern the focus only on a diagnosis of depression.

The diagnosis of posttraumatic stress disorder (PTSD) was not included in the article although 125 subjects experienced the sudden death of a spouse, an event that is outside the ordinary experience of most of such subjects. The non-*DSM-III-R* diagnosis of pathological grief reaction was also not considered. Some depressions may be pathological grief reactions, others may be cyclical depressive disorders brought forward by the experience of a stressful life event in a predisposed person. It is very important in understanding cases and diagnoses to consider such parameters. In future studies it would be a good idea to assess the signs and symptoms of PTSD, including intrusion and avoidance symptoms, as well as to assess depressive signs and symptoms.

In research such as that on the consequences of losses, it is important to formulate each case and also to make every diagnosis that is appropriate to the subjects. To focus on one diagnosis may ignore the multifaceted nature of pathological grief, which may present as increased anxiety symptoms, increased depressive symptoms, psychosomatic disorder, increased mixtures of anxiety and depressive symptoms, and PTSD symptoms such as those of unduly prolonged or intense intrusion or denial.

The authors stated that "one of the long-range goals of the San Diego Widowhood Project is to develop treatment strategies based on a sound understanding of the natural history and course of bereavement." They cited several treatment modalities, including the brief psychodynamic-cognitive therapy for stress response syndromes developed at the University of California, San Francisco. They stated, "None of these is specifically geared to treat or prevent depression in the bereaved." As it happens, the University of California, San Francisco, treatment was developed in the context of treating subjects with traumas and/or pathological grief reactions. Depression is not the only diagnosis from *DSM-III-R* that applies to pathological grief reactions, and the treatment should be applied to the etiology, not the descriptive, formal diagnosis.

I think this is an outstanding study, a forward-moving effort in the study of the consequences of bereavement. I do think that study of treatment for a subtypology such as the combination of bereavement and major depressive disorder without PTSD or other diagnoses will be useful. I only wish to point out our present problem of how to "officially" diagnose pathological grief. Our present nomenclature has no set of categories for disorders caused by serious life events combined with dispositional factors. Of interest, in this domain we may soon be able to move from descriptive to etiological classifications.

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### Dr. Zisook and Dr. Schuchter Reply

SIR: We fully agree with Dr. Horowitz that grief is multifaceted and that our field needs to develop more valid and reliable ways of defining pathological grief reactions. Dr. Horowitz correctly points out that we did not include the diagnosis of PTSD in our study. However, our reading of the *DSM-III-R* criteria for PTSD is that spousal bereavement generally does not satisfy criterion A (p. 250). The boundaries between "uncomplicated bereavement" and some of the potential complications of bereavement, such as PTSD and major depressive disorder are not as well demarcated as we hope they will be by the time future editions of *DSM* come along. We also agree with Dr. Horowitz that depression is only one of several possible pathological outcomes of loss and that in future studies it would be a good idea to assess signs and symptoms of PTSD as well as symptoms of other anxiety disorders. An ideal outcome study would include not only the Impact of Events Scale (1) but also comprehensive diagnostic interviews with detailed past histories, personal resources, and intercurrent life events, and matched married control subjects. Such a study could substantially help clear up some of the aforementioned boundary problems.

Dr. Horowitz's comments prompted us to do an additional analysis. We divided the sample into subjects whose spouses' deaths were "sudden and unanticipated" (N=121) and those whose spouses' deaths were "prolonged and unanticipated" (N=168); outcome measures included depression as well as scores on nine subscales of the Hopkins Symptom Checklist (HSCL) (2) 2 months after the loss. There were no significant differences between groups in the percentage of subjects who met criteria for a depressive syndrome (24% versus 23%) or on the interpersonal sensitivity, hostility, obsessive-compulsive, paranoid, psychotic, or somatization subscales of the HSCL. On the other hand, the group whose spouses died suddenly and unexpectedly had significantly higher mean scores on the subscales for depression (1.87, SD=0.61, versus 1.70, SD=0.50; $\chi^2$=6.50, df=1, p=0.01), anxiety (1.7, SD=0.66, versus 1.55, SD=0.55; $\chi^2$=6.87, df=1, p=0.009), and phobia (1.34, SD=0.50, versus 1.19, SD=0.32; $\chi^2$=8.95, df=1, p=0.003). Thus, there are differences in outcome based on the type of death; when death occurs suddenly and unexpectedly, it is likely to be experienced as more traumatic, subsequently evoking more depressive, anxiety, panic-like, and avoidant symptoms.

We are in less agreement with Dr. Horowitz's statement that treatment should be applied to the etiology, rather than the descriptive, formal diagnosis, in pathological grief reactions. There are some data to suggest that major depressive syndromes, even when they occur in the context of bereavement, may respond well to antidepressant medication. In such cases, phenomenology may be at least as important as etiology in the selection of treatment, although neither should be ignored. However, we also feel that only well-designed, controlled studies comparing the major treatment options and combinations thereof will resolve this issue.

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### Depression in Borderline Patients Who Split

SIR: Updating an earlier report on the comorbidity of borderline personality disorder and depression, John G. Gunderson, M.D., and Katharine A. Phillips, M.D. (1) considered several hypotheses relating the two pathologies, then concluded that "a surprisingly weak and nonspecific relationship exists between these disorders." In essence, they maintained that depression and personality disorder are somewhat distinct phenomena and not psychologically or biologically linked. I propose that, at least for borderline patients who use the splitting defense (2), depression and personality structure are indeed related and that the link is most likely both psychological and biological.

Why are borderline patients, particularly those who split, so prone to severe, debilitating depression, sometimes leading to mood-driven psychosis, in the face of negative experience? In part, most likely, because splitting makes it difficult for these patients to acknowledge a disappointment or loss for what it is and work it through. By creating a split self unit and a split object (other person) unit, by "dis-integrating" the ambiguity of self and other—i.e., their reality—it is possible to keep polar opposite representations of self and other separate in consciousness and so sidestep the anxiety of having to deal with the "whole" situation all at once.

To come to terms with a loss or disappointment, the initial meaning of what was lost must first be acknowledged and lived. But this is precisely what splitting borderline patients cannot do, because it requires accepting the ambiguity of the situation in lived consciousness. Attempting to deal with a loss, these patients continue to oscillate between positive and negative meanings of it, perceiving the lost possibility or object first as all good, then as all bad, embracing only half the reality in each oscillation. Such defensive maneuvering, skating around any stable meaning, makes coming to terms with the lost possibility or object impossible.

It seems likely that the way the world is perceived in response to negative experience is a more complex phenomenon for a splitting borderline patient than for someone without this pathology and that the consequent depression of the borderline patient would be more profound and difficult to reverse. Differences in the nature of depression in borderline and nonborderline patients have been noted, and the latter group is known to be less responsive to antidepressants and lithium (1). Adding to all this the possibility that borderline splitting may itself have a neural basis (3), it seems reasonable to leave open to further empirical test the question of whether depression in borderline patients who split is psychologically and biologically related to the personality disorder.

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## Borderline Personality Disorder and Depression

SIR: A recent article by John G. Gunderson, M.D., and Katharine A. Phillips, M.D. (1) overstated the differences between borderline personality disorder and depression. Specifically, the overlap between borderline personality disorder and certain forms of nonendogenous or atypical depression received insufficient attention. While the authors mentioned hysteroid dysphoria, a form of atypical depression, they failed to note several important findings. Parsons et al. (2) showed that atypical depressive subjects who also met borderline personality disorder criteria were more selectively responsive to monoamine oxidase inhibitors (MAOIs) than those who did not, and that phenelzine response rates in the former group were in the 90% range. Also, Liebowitz et al. (3) found that borderline personality features per se in atypical depressive subjects improved to a significantly greater extent with the MAOI phenelzine than with the tricyclic imipramine or placebo, suggesting that borderline features in this population are affectively mediated.

In general Dr. Gunderson and Dr. Phillips are correct that borderline personality disorder can be readily distinguished from melancholic or endogenous forms of depression that are highly responsive to tricyclics. However, the relationship of borderline personality to more specifically MAOI-responsive atypical forms of depression is still uncertain, and the overlap appears substantial. To minimize this is to risk undertreatment of potentially MAOI-responsive borderline patients.

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## Dr. Gunderson and Dr. Phillips Reply

SIR: "The practical hazard of hypothesis III [that borderline personality disorder and depressive disorders coexist but are otherwise unrelated] is that patients with the borderline syndrome sometimes respond partially and occasionally respond dramatically to antidepressants, suggesting that clinicians should not rule out use of this treatment" (p. 974 of our article). We made this statement despite the overwhelming data indicating that there is no relationship between these disorders because, from a clinical and conceptual standpoint, we favored a more complex interactive model with its possibility of shared etiologic sources. In this regard, we are grateful for Dr. Liebowitz's letter, buttressed by two references of which we were unaware, in which he offers some substantiation of our preferred model.

On a different level, Dr. Liebowitz's letter should be seen as expressing the concern of a psychopharmacologically oriented psychiatrist who fears that the subgroup of borderline patients who may respond to MAOIs will go unrecognized and be unnecessarily mistreated. This widely acknowledged concern has its battered counterpart in the concern that, in the search for a pharmacological cure, the majority of borderline patients (who show only modest or even no response to medications) will be misguided by an expectation for rapid change and deflected from recognizing the importance of the psychosocial sources of their difficulties (e.g., neglect and abuse) and the possible value of psychosocial treatments (e.g., psychotherapy, Alcoholics Anonymous, family therapy). However undocumented their effectiveness, such psychosocial treatments address the issues essential to the longer-term welfare of borderline patients.

A naive reader might conclude from Dr. Liebowitz's letter that it has now been established that MAOIs have substantial benefits for many, even most, borderline patients. Yet, Cowdry and Gardner (1), who conducted the only direct test of MAOIs on a rigorously defined sample of borderline patients (unlike the two references cited by Dr. Liebowitz), reached a far more modest conclusion: "It is critical that the medication trials be a collaborative effort between patient and physician and that the medication be understood by all as an adjunctive treatment modality that is likely to be of limited benefit rather than a magic potion or panacea" (p. 118).

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## ECT Response in Catatonia

SIR: Michael Smith, M.D., and Breck Lebegue, M.D. (1) described a man with severe chronic catatonia who did not respond to 20 ECTs or sequential trials of several pharmacological agents but who showed clinical improvement on a regimen of 20 mg/day of lorazepam. The lack of response surprises us in view of the reported experience (2, 3) of the successful treatment of catatonia with ECT. Further details of the ECT are needed. Specifically, we need to query whether the treatments were adequate, by examining such elements as concurrent medication (especially benzodiazepines), electrical dosage, seizure threshold, electrode placement, and duration of the seizures (4).

Unless seizures are monitored for adequacy there is no assurance that "treatment" was actually done. The APA task force report (5) argues that if the response to six to 10 treatments is insufficient, modification of ECT technique should be considered, including "switching from unilateral to bilateral ECT, increasing stimulus intensity levels, and using medications to potentiate the ictal response" (p. 103). Additionally, early workers used percent time in slow wave EEG activity or sedation threshold as an index of treatment efficacy (6).

Thus, until the reader is assured that the ECT in this case was adequately administered, the expressed view that a catatonic patient failed to respond to ECT should be questioned, as the evidence for efficacy of ECT in this syndrome is compelling.

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## Dr. Smith Replies

SIR: I thank Drs. Francis and Fink for underscoring an important consideration in the treatment of catatonic schizophrenia.

In answer to their query, the following information is provided. Mr. A had a total of 20 ECTs, 11 of which were with bilateral lead placement. The total seizure time, as determined by observed tonic-clonic muscle activity, was 661 seconds, with an average seizure time of 33 seconds. The longest seizure was 54 seconds, the shortest was 20, the standard deviation was 11 seconds. Additional parameters included a pulse width of 1.5 msec, stimulus duration of 2.0 seconds, and a frequency of 70 Hz. The treatments were given over a 49-day period, averaging one treatment every 2.5 days. At the time of the first ECT, Mr. A was being treated with lorazepam (1 mg/day), as well as haloperidol (10 mg/day). The lorazepam was discontinued after the second treatment and was reinitiated after the ninth treatment, as a result of Mr. A's increasing agitation, at a dose of 3 mg/day. It was continued at that dose through the remaining ECTs. Seizure-enhancing medications (e.g., caffeine) were not utilized.

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## GABA-Benzodiazepine Receptors

SIR: I would like to compliment Charles F. Zorumski, M.D., and Keith E. Isenberg, M.D., on their elegant article (1). The authors provided a thorough review of the relationship of centrally acting benzodiazepines to the $GABA_A$ macromolecular complex and associated ion channel. As the title suggests, they incorporated considerable insight into the possible mode of action of GABA-related compounds and provided cogent explanations of, and support for, the functional significance of cited observations. Despite the article's eloquence, there was an error, possibly stemming from an apparent oversimplification regarding drug actions at benzodiazepine receptor subtypes, which warrants attention and correction. The original studies of the $BZ_1$ selectivity of CL 218872 (a triazolopyridazine) suggest that $BZ_1$ receptors are primarily associated with an anxiolytic response as opposed to other benzodiazepine-related effects (e.g., sedative-hypnotic). These conclusions, however, remain largely unsubstantiated and may reflect the unique properties of CL 218872 more than a general action mediated by $BZ_1$ receptor sites. Other classes of compounds such as the imidazopyridines (zolpidem) and the pyrazoloquinolines are also $BZ_1$ receptor selective but are known for their sedative-hypnotic as opposed to anxiolytic characteristics. The only $BZ_1$ selective sedative-hypnotic currently available is quazepam (2–6).

Quazepam is marketed under the trade name Doral. Drs. Zorumski and Isenberg erroneously employed quazepam as an example of a $BZ_2$ selective agent. Clearly, this is not the case. Although molecular biological studies indicate there are more than just two central benzodiazepine receptor subtypes, quazepam still relates more closely to what has been classically defined as $BZ_1$ rather than $BZ_2$ receptor activity. The theory that $BZ_1$ receptor activation is exclusively involved in sleep mechanisms is likely to prove to be an oversimplification as well, but, as pointed out by Drs. Zorumski and Isenberg, such hypotheses serve as heuristic starting points for the development of effective therapeutic agents with fewer side effects. As a scientist committed to elucidating quazepam's activity at central $BZ_1$ sites, and on behalf of my colleagues working in this area, I hope that this inaccuracy will be corrected.

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## Dr. Zorumski and Dr. Isenberg Reply

SIR: Dr. Wamsley raises an interesting and important point regarding drug actions at the $GABA_A$-benzodiazepine receptor. He contends that quazepam is selective for the benzodiazepine $BZ_1$ subtype of receptor. An important goal of current pharmacological research, as Dr. Wamsley notes, is to elucidate the site at which drugs exert their effect on the $GABA_A$ receptor. A purpose of our review was to indicate to readers the surprising number of GABA receptor subunits, all of which could function as sites of action for various drugs. Other reviewers, noting the proliferation of $GABA_A$ receptor subunits, calculate the potential magnitude of receptor complexity (1). Current pharmacological typing underestimates actual receptor complexity. Future work, integrating pharmacological and physiological approaches with molecular techniques, will better define the site of action of currently available drugs as well as offer the promise of more specific agents for the treatment of psychiatric disorders.

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## Mania and AIDS

SIR: The article by Karl Kieburtz, M.D., and his colleagues (1) described eight AIDS patients who developed mania at some point after HIV infection. The authors stated, "No cause for a secondary affective disorder other than HIV infection was identified." However, they did not mention how they determined that the manic episode was not due to zidovudine (five patients were taking zidovudine prior to admission) or to antidepressant therapy (four of five patients with histories of depressive disorder were treated with antidepressants), both of which are known to cause manic symptoms (2, 3). Since this population is known to have more frequent and severe side effects from standard pharmacotherapies, clarification of this point would be helpful.

In addition, because primary affective disorders can occur at any age, it is possible that some patients could have been at higher risk for developing a mood disorder regardless of, or in addition to, any physical disorder. Information regarding any family psychiatric history may help substantiate or refute the likelihood of such an occurrence.

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SIR: Dr. Kieburtz and associates suggested that AIDS causes mania. Additional mechanisms might explain the increased prevalence of mania in their AIDS population and would also predict an increased prevalence of HIV infection among patients with manic presentations. First, crack and intravenous cocaine abuse, which increase the risk for HIV and syphilitic infection (1), can themselves present as mania and can exacerbate preexisting mania (*DSM-III-R* and 2). Mania from cocaine, affective illness, or a combination of these can persist even after urine testing for recent cocaine use has become negative. False negative urine testing can also occur. Recent users of large amounts of cocaine were locked into a drug-free unit and given two types of urine tests. Thirty-seven percent had a negative urine test preceded and followed by a positive test on one or both tests (3). Second, mania as a primary disorder is associated with the behaviors of hypersexuality and substance abuse (*DSM-III-R* and 2), which are risk factors for HIV and syphilis. Substance abuse has been repeatedly linked to sexual risk-taking behaviors that increase the risk for sexually transmitted diseases, including HIV infection (1). Neurosyphilis, which is possibly on the increase, is associated with HIV infection and it can present with mania. Symptomatic HIV infection gives serum syphilis tests a higher false negative rate (4).

Since the presence of HIV risk factors is often denied, we propose strong consideration of HIV testing in manic presentations, especially when the patient is 30 years old or older or presents with hypersexuality, even when a urine test for detecting cocaine use is negative. Thirty is the minimum age for stronger consideration of HIV testing on the basis of the epidemiology of cocaine abuse and affective illness and the average age of 37 for Dr. Kieburtz and associates' patients. Cocaine abuse usually begins in a patient's teens or 20s (*DSM-III-R*), so by age 30 many crack or intravenous cocaine abusers will have used these drugs long enough to increase their HIV risk. Bipolar and schizoaffective disorders can present in adolescence, although usually their onset is in the third decade (*DSM-III-R*). Therefore, many bipolar and schizoaffective patients will have had enough previous manic episodes by age 30 for the hypersexuality and substance abuse of mania to increase their HIV risk. We suggest that other etiologies for the mania associated with HIV infection be considered before concluding that HIV itself causes mania.

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## Dr. Kieburtz and Dr. Caine Reply

SIR: These letters reflect the difficulty in establishing the cause of a secondary affective disorder. As we described in our article, we chose to follow specific a priori criteria for establishing that in these patients a manic syndrome was secondary to HIV infection. These criteria included the fact that the patients presented with a characteristic manic syndrome and demonstrated coexisting or emerging cognitive impairment. Additionally, there was laboratory evidence of active cerebral disease, as well as evidence of active immunosuppression. Furthermore, we evaluated the patients comprehensively for other causes of secondary mania, although given the space limitations we did not describe all the negative testing or unrevealing assessments. We could identify no well-established cause of a secondary affective disorder other than HIV infection in these patients. This search included consideration of prescribed medicines, over-the-counter medications, and substances of abuse. Additionally, secondary infections and other medical causes of mania were excluded.

Regarding the comments by Dr. Holmes, zidovudine has not been convincingly shown to cause a secondary mania. The reference cited by Dr. Holmes was a letter to the editor that presented two case reports. It would be difficult to establish a causal relationship based on these limited data. In our patient, there was certainly no temporal relationship between zidovudine therapy and the development of manic symptoms. Additionally, the one patient who began taking zidovudine during hospitalization for the manic syndrome showed no adverse effects from this medication. In response to Dr. Holmes' other question, five patients had a prior history of an affective disorder, as stated in the article. Four of these patients had been treated with antidepressants in the past, but at the time of their manic syndromes none of the patients was receiving such therapy. Four of these same five patients also had family histories of affective disorder, with depression in three families and a history of bipolar disorder in one.

Regarding the comments by Dr. Whitefield and associates, all patients were screened for drugs of abuse. Similarly, all patients were tested for the presence of syphilis. Admittedly, these tests may be imperfect; however, the laboratory tests were only one element in our clinical evaluation of each subject. On the basis of our examination and knowledge of these patients, we could find no evidence that their mania was caused by cocaine abuse or syphilis. All of these patients were well known either by colleagues or the authors before their psychiatric inpatient admission, or they were followed after discharge. No clinical data have substantiated an abuse-related etiology for their mania. Furthermore, the likelihood of these tests being falsely negative for the entire group of eight patients was particularly unlikely.

Our data did not support the recommendation that patients with mania be tested for HIV routinely. All of the patients we described had progressed to AIDS by the time their mania developed. Their primary diagnosis of HIV infection was obvious due to their opportunistic diseases. It has not been our experience that the manic syndrome occurs early in HIV infection or in otherwise asymptomatic patients.

We also strongly advocate the vigorous search for other secondary causes of mania before concluding that a patient with AIDS has mania due to HIV infection. It has been our experience that there is usually additional evidence supporting this diagnosis, e.g., meningeal enhancement on magnetic resonance imaging or emerging cognitive impairment. Thus, patients should fulfill the full array of criteria for establishing a secondary syndrome before concluding that their mania is due to HIV infection.

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## Blunting of Clonidine-Stimulated Growth Hormone Release in Mania

SIR: In their excellent article showing blunted growth hormone (GH) stimulation in response to desipramine, Timothy G. Dinan, M.D., M.A., and associates (1) stated that to their knowledge, GH reponses to noradrenergic challenges have not been previously investigated in mania. In fact, my colleagues and I have already shown a similarly blunted GH response to clonidine (0.15 mg i.v.) in seven drug-free manic patients age- and sex-matched to seven inpatients with major depression and seven with minor depression (2). The mean GH peak was similar in the manic patients (3.2 ng/ml, SD=2.4) and in the patients with major depression (3.2 ng/ml, SD=2.4) and significantly lower than in the subjects with minor depression (13.2 ng/ml, SD=8.7).

Results of these two studies support the hypothesis that $\alpha_2$-receptor abnormalities represent a trait marker for affective disorder. Another important consideration in interpreting these results is that the increased receptor sensitivity hypothesized to be related to mania (3) would be expected to peak in the later phases of bipolar depression before the "switch" to mania and to attenuate after the onset of the manic episode as receptors down-regulate in response to increased catecholaminergic availability. In fact, the only suggestion of augmented GH responses to clonidine challenge has been found in bipolar depressed patients (4). Therefore, the results of these two studies do not suggest sustained increases in $\alpha_2$-adrenergic receptor sensitivity in mania but cannot address the apparently more physiologic hypothesis advanced by Bunney et al. (3) that receptor increases precede the "switch" to mania, since the patients were evaluated at least several weeks after the onset of the manic episode. Obviously, the evaluation of the "switch" hypothesis needs longitudinal studies of bipolar patients.

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## Challenge for Psychiatry

SIR: The editorial by Allan Beigel, M.D. (1) was timely. It brought to our attention how our profession can be used by government for motivations other than patients' care. The beauty of the editorial, if I understood it correctly, is that while recognizing the plight of our colleagues in Eastern Europe who worked for years under the Communist ideology, it also called for our attention to problems of a similar nature in this country.

Dr. Biegel mentioned the dilemmas faced by psychiatrists in the United States who are asked to work in less than satisfactory conditions and to abide by ideologies that do not always make patients' care the first priority. I am thinking here of the public psychiatrists in America, often foreign medical graduates without many options of employment, who must accept impossible case loads of patients housed in totally improper therapeutic environments and even who are pressured to discharge these patients to the streets, to become homeless. I am also thinking of the psychiatrists in the private sector who , in order to survive economically, are being asked to abide by an "ideology of the brain" that is robbing the American psychiatric patient of his or her soul.

I have nothing against psychiatrists in the United States extending a hand to help our Eastern European colleagues to move to a different political system. But let us not forget that charity begins at home and that maybe now is the time for American psychiatrists to lose their fears of speaking out against policies, government or private, that are contrary to the promotion of mental health.

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*Reprints of letters to the Editor are not available.*

# Position Statement on Day Care for Preschool Children

*This statement was prepared by the Task Force on Day Care for Early Pre-School Children[1] of the APA Council on Children, Adolescents, and Their Families. It was approved by the Assembly of District Branches in November 1991 and by the Board of Trustees in December 1991.*

The American Psychiatric Association recognizes that the early development of children has a profound impact on later psychological development and the potential of individuals. Practicing psychiatrists are confronted directly and indirectly with questions related to child care through their involvement with families. The psychiatrist, as physician, is able to integrate the knowledge and skills needed in understanding the biopsychosocial dimensions that arise for all concerned with child day care. The Task Force on Day Care for Early Pre-School Children is cognizant of the debate on the merits of day care, the controversy about its impact on development, and the absence of comprehensive criteria to assess day care quality.

Research indicates that the infant-parent relationship is a fundamental cornerstone of infant development: a secure attachment to ongoing caregivers (most often parents) has been identified as a necessity for psychological and emotional development. Infants who are securely attached to their caregivers are more socially competent than infants who have not developed secure attachments.

Other research indicates that when parents can take advantage of leave from work, infant-parent attachment is enhanced. Demonstration of those findings required a minimum of 4 months of leave, but further research may be able to better pinpoint the crucial developmental times when such added parental presence is particularly helpful. Clearly, whether parents are in professional or occupational training or in the general work force, special considerations are vital to support parenting functions.

There is evidence that good-quality day care for preschool children in vulnerable populations has a *positive* developmental outcome. Additional research has documented that poor-quality care has detrimental developmental consequences for infants and young children. Better working conditions for child care providers correlates with stability of staff and continuity of day care offered to the children, both important variables in quality care.

Often child care by persons other than parents is not a matter of choice. Thus, both government and the private sector must respond to this reality. To assure the well-being of children and the facilitation of the family, the developing body of information about the influences on health development must be considered. Whether traditional family care or child day care, it is the quality of care that is crucial.

Primary developmental issues are significant throughout the preschool years, and they increasingly involve not only the parents but also other caregivers and peers. At the same time that interpersonal relationships increase in complexity, maturing youngsters also solidify their intrapsychic development. Day care provides a special opportunity for enhancement of or interference with development. Good preschool day care incorporates attention to all health care issues, alertness to hazards of traumatic experience (including abuse), and special attention to individual needs related to physical illness, handicaps, and cultural and ethnic uniquenesses. As psychiatrists, we are particularly aware that the absence of attention to these important factors in child development can lead to psychopathology, both in childhood and in adult life. Therefore, the American Psychiatric Association adopts the following policies:

1. The American Psychiatric Association, with other national organizations, shall advocate for the right of children to have developmentally appropriate care in a safe and caring environment.
2. The American Psychiatric Association believes that the assurance of quality care through a variety of means is essential for the healthy development of children. The adoption of developmentally appropriate day care standards is integral to the achievement of quality care.
3. The American Psychiatric Association will work with other professional organizations and consumer groups to help inform parents and other utilizers of child care about the issues of quality day care.
4. The American Psychiatric Association and its district branches, with other appropriate groups, will work to recognize the professional role of child care workers and the importance of appropriate compensation and provision of career incentives. The continuing development of training curricula for child care workers, with sensitivity to cultural diversities, is essential.
5. The American Psychiatric Association recognizes that certain populations may require special consideration in the development of day care standards. Additional educational and supportive services may be desirable to provide adequately for the care of, for example, children of single parents or two-job employees or children who are mentally or physically disadvantaged.
6. The American Psychiatric Association urges the adoption of policies, by all appropriate parties, that will allow the type of parental leave options, including part-time training and employment, that will enhance mother-infant bonding and the facilitation of the family. The absence of appropriate parental leave policies places children and families at risk for adverse psychological development.
7. The American Psychiatric Association urges increased research on the impact of day care on preschool children. Research is needed within the ecology of day care, not only focusing on the child per se but also extending to the potential consequences for the family system and for our society.

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[1] The task force members are Myron L. Belfer, M.D. (chairperson), Shahla Chehrazi, M.D., Shaila Misri, M.D., Aubrey W. Metcalf, M.D., Nancy W. Stone, M.D., Moira V. Kennedy, M.D. (Member-in-Training), and Thomas G. Webster, M.D. (consultant).

THE AMERICAN JOURNAL OF PSYCHIATRY

*Special Articles*

# Gender Differences in Pharmacokinetics and Pharmacodynamics of Psychotropic Medication

**Kimberly A. Yonkers, M.D., Judith C. Kando, Pharm.D., Jonathan O. Cole, M.D., and Susan Blumenthal, M.D., M.P.A.**

*Objective: This review explores the theoretical background for and empirical evidence supporting gender-related differences in pharmacokinetics and pharmacodynamic properties of psychotropic medications. Method: The authors reviewed all English-language articles on this topic that involved original research using human subjects. Results: Limited evidence suggests that young women seem to respond better to and require lower doses of antipsychotic agents and benzodiazepines than young men. The administration of exogenous hormones interacts with medications, changing plasma levels and possibly conferring greater risks for toxicity. Young women may have an enhanced response to nontricyclic antidepressants. Conclusions: Too little basic and clinical research has been conducted on sex differences in therapeutic effects and side effects of psychopharmacological treatments. Addressing these differences as well as similarities will lead to safer and more effective treatment for all patients.*

(Am J Psychiatry 1992; 149:587–595)

As effective pharmacological treatments are found for many psychiatric disorders, psychiatrists have become acquainted with the nuances of prescribing such treatments. Pharmacological research is a guide for psychiatrists as they weigh therapeutic effects against side effects or potential adverse reactions. Research reveals sources of variability in therapeutic properties and adverse effects of medications (pharmacodynamics) and the amount of drug available for therapeutic action after administration (pharmacokinetics). One important source of variability to be considered is the sex of a patient. Phase I studies, which determine therapeutic doses, are conducted with male subjects, but women seek treatment and receive psychotropic medication more frequently than men (1, 2).

There are theoretical reasons to suggest gender-related drug effects, and there are limited clinical data to support such hypotheses for different psychopharmacological agents. In this paper we explore the theoretical reasoning behind sex differences in pharmacokinetics and pharmacodynamics of psychotropic agents. We then summarize the literature on this topic as it pertains to psychotropic medications. It is our hope that this summary will disseminate what is known about gender-related differences in psychopharmacological agents and encourage thought for areas of future exploration.

## POTENTIAL SEX DIFFERENCES IN PHARMACOKINETICS

### *Absorption and Bioavailability*

The percentage of drug that is absorbed from the gastrointestinal tract depends on the acid base and lipophilic properties of the drug as well as the physiology

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of the gastrointestinal tract. The degree to which a drug is ionized affects its solubility. It has been suggested that women secrete less gastric acid than men, leading to potential gender differences in absorption (3). There are also several studies indicating such differences in gastric emptying. Wald et al. (4) examined gastrointestinal transit time in women during the menstrual cycle, once in the follicular phase, when progesterone levels are low, and once in the early luteal phase, when progesterone levels rise. They found that transit time was prolonged significantly in the luteal phase. However, a study using a different method conducted by Horowitz et al. (5) yielded conflicting results. Horowitz et al. concluded that progesterone caused slowing in the small intestine during the luteal phase. Datz et al. (6) undertook a study to determine if nonpregnant women empty solids and liquids differently from men. They found that women empty both solids and liquids more slowly. The mechanism for the difference is unknown, but Datz et al. proposed that it is the effect of progesterone and estradiol on the gastrointestinal tract.

These findings suggest that gonadal hormones may play a role in changing absorption rates, which can affect bioavailability. Bioavailability is the fraction of administered dose that reaches the patient's systemic circulation (7). If the bioavailability of a drug given to women is substantially altered, the dose will need adjustment in order to achieve a comparable concentration in the plasma.

Given the many variables that need to be considered, it is difficult to determine the specific effect of less gastric acid secretion and slower gastric emptying. One can speculate about several possibilities, however. For example, most absorption occurs through the intestinal mucosa. A smaller degree of absorption occurs in the acidic stomach, where enzymatic and mechanical activities digest and break down larger compounds. Since enzymes can denature proteins, an increase in the speed of gastric emptying generally decreases exposure to enzymes and increases the opportunity for absorption in the intestine (8). Thus, a lower gastric emptying rate during the luteal phase, as suggested by Wald et al. (4), would ultimately decrease the amount of drug absorbed. However, if transit time is prolonged in the intestine, as Horowitz et al. (5) suggested, the opposite would occur.

By maintaining the necessary acidic environment for enzymatic action, gastric acid secretion adds an additional variable to the absorption equation. For weak acids, an acidic environment establishes a nonionic state. This enhances their absorption because compounds require neutralization in order to be absorbed through a nonpolar lipid bilayer. Conversely, if the acidic environment is maintained, absorption is decreased for weak bases because they remain ionized. A decrease in gastric acid secretion, as noted in the study of Grossman et al. (3), may decrease enzymatic action and decrease the absorption of weak acids but increase absorption of weak bases.

These possibilities are simplified and provide just an outline of hypothetical sex-related or menstrual cycle variations in absorption. These effects are complicated and may counterbalance one another; ascertainment of gender-related differences in bioavailability will ultimately require empirical studies of different compounds.

### *Distribution*

The physical and chemical properties of a drug determine its distribution. These properties include acid base, water and lipid solubility, and affinity for binding proteins (9). Changes in vascular volume and tissue volume also alter the distribution of a drug (8). If the volume of distribution of a drug is changed, the loading dose and the dosing interval during therapy might have to be modified.

The ratio of lean body mass to adipose tissue mass can also affect a drug's disposition. In general, females have a lower ratio of lean body mass to adipose tissue (10). Drugs with a high affinity for adipose tissue (e.g., diazepam), would be expected to demonstrate a greater volume of distribution in females. Other factors that affect the volume of distribution include differences in blood volume, cardiac output, and organ size (8). Drugs that have a greater volume of distribution would probably have a lower serum concentration when first administered. Over time, however, the potential for storage of medication in adipose tissue is higher. Thus, half-life may become prolonged and serum levels may be greater in patients with less lean body mass. The effect of sex on these factors in relationship to specific drugs has not been adequately studied.

### *Metabolism*

The hepatic drug metabolizing enzymes play an important role in the removal of many drugs from the systemic circulation. Drugs may undergo either phase 1 or phase 2 metabolism. Phase 1 metabolism consists of oxidation, reduction, and hydrolysis; phase 2 metabolism consists of glucuronidation and sulfation. Hepatic extraction is the amount of medication that is removed from the systemic circulation by the liver. Drugs with a high hepatic extraction ratio are sensitive to hepatic blood flow rather than hepatic enzyme activity. Antipyrine, a substance with a low hepatic extraction ratio, is often used to evaluate the oxidative function of the liver (11). Studies examining the effect of gender on the plasma half-life of antipyrine have produced conflicting results. Riester et al. (9) and Fraser et al. (12) found no difference between men and women, but O'Malley et al. (13) found that the antipyrine half-life was 30% longer in men than women, thus supporting a gender-specific difference in oxidative function for this drug. However, O'Malley et al. did not control for smoking and menstrual cycle effects and Riester et al. did. This probably accounts for these discrepancies. Studies examining gender differences in phase 1 and phase 2 metabolism are needed to clarify this issue.

The liver is also responsible for first-pass metabolism. The first-pass effect occurs when a drug is absorbed from the gastrointestinal tract into the portal circulation. Drugs are then extensively metabolized in the liver before they reach the systemic circulation (7). The systemic clearance of drugs that undergo extensive hepatic metabolism are sensitive to changes in hepatic blood flow. Studies examining gender differences in hepatic blood flow are lacking.

### *Menstrual Cycle Effects*

There are several possible menstrual-phase-specific changes such as those involving gastric motility. Although studies confirming changes in weight across the menstrual cycle are inconsistent, a subgroup of women do experience water retention (14). Potential changes may include increases and decreases of the volume of distribution. One study found evidence of menstrual phase changes in transcapillary fluid dynamics, resulting in fluid shifts between intravascular and extravascular spaces (14). Again, empirical studies are lacking, but an increase in fluid retention may dilute the concentration of medications, resulting in lower plasma levels. Of course, the amount of fluid retained would have to be quite large. The opposite would occur if fluid shifts favor extravascular volume increases.

Changes in the activity of hepatic microsomal oxidase systems may occur depending on the cycle phase and levels of progesterone and estrogen (15). Monamine oxidase activity may be decreased by estrogens and increased by progesterone (16, 17). There is also evidence that exogenous ovarian hormones affect the metabolism of medications. In a study looking at women's capacity to complete cognitive and behavioral tasks (e.g., driving an automobile), Ellinwood et al. (18) found that women taking oral contraceptives and a standard dose of diazepam throughout the menstrual cycle were relatively "intoxicated" during the menses. By showing that the same oral dose of a benzodiazepine had a more potent effect during one part of the menstrual cycle, these authors demonstrated that the pharmacodynamics of the benzodiazepine changed across the cycle. This highlights the importance of establishing menstrual cycle phase when investigating pharmacodynamic as well as pharmacokinetic properties of psychotropic medications.

## SEX DIFFERENCES IN PSYCHOTROPIC AGENTS

### *Antipsychotic Agents*

The literature analyzing pharmacokinetics, pharmacodynamics, and side effects of psychotropic agents by sex is the most substantial for antipsychotic drugs (table 1). Several researchers have found higher plasma levels of antipsychotics in female subjects (20, 21). Simpson et al. (20) found higher fluphenazine levels in women despite comparable dosing and similar age and weight characteristics. Chouinard et al. (21) investigated fluspirilene, a long-acting injectable neuroleptic, and found that women required roughly half the doses required by men despite similar weight and age characteristics. In this trial, the prescribed doses were titrated to therapeutic efficacy. Unfortunately, serum levels were not reported.

Antipsychotic drug levels were reported in another recent study that explored the relationship among thiothixene levels, demographic variables, and drug interactions (22). Men had significantly higher oral clearance than women; clearance did not necessarily correlate with body weight. The authors also found a reduction in clearance for subjects over the age of 50. They did not say whether factors of smoking and concurrent use of enzyme-inducing drugs overrode these demographic variables.

Rather than using explanations based on pharmacokinetics, several authors have suggested that properties of ovarian hormones may modify and improve the efficacy of antipsychotic treatment in women. Chouinard and Annable (19) found that women had greater improvement than men after treatment with pimozide and chlorpromazine. The weights of the men and women were equivalent, as were the doses prescribed. Chouinard and Annable (19) hypothesized that the greater efficacy in young women was due to the presumed antidopaminergic effect of estrogen (27, 28).

Several authors (23, 24) invoked antidopaminergic properties of estrogen to explain why young women are prescribed lower average doses of antipsychotics than are young men. These researchers assumed that the level of medication prescribed reflects the amount of medication required for a therapeutic response. Given that assumption, these authors suggested that premenopausal women receive additional antipsychotic benefit. In addition to the possibility that estrogen's dopamine-receptor-binding activity contributes to antipsychotic efficacy, it has recently been shown that progesterone may have a role in inducing behavioral changes (29). Several major metabolites of progesterone bind to the $\gamma$-aminobutyric acid receptor complex (29). Depending on the metabolite, they provoke agonist and antagonist activities.

The possibility of gender differences in the actions of antipsychotic medications is also implied by the variable expression of antipsychotic-induced side effects. It has been suggested that the incidence of tardive dyskinesia is greater in women (25, 26, 30). Smith et al. (25, 30) found that the severity of tardive dyskinesia was far greater in women over the age of 67. Chouinard's group (26) also reported that young men in their sample had a higher prevalence of severe dyskinesias than women. In a subsequent letter (31), they explained this discrepancy by suggesting that postmenopausal status and loss of estrogen-induced supersensitivity may favor the development of tardive dyskinesia in postmenopausal women. If estrogens were acting in some way at dopamine receptors, it would be consistent with a protective effect for premenopausal women.

The literature comparing the action and side effects of antipsychotic agents supports gender-related dissimilarities in plasma levels and side effects as well as the possible therapeutic advantage of these agents. Again, the assumption that the dose prescribed is the required

**TABLE 1. Literature Analyzing Gender Differences in Pharmacokinetics, Pharmacodynamics, and Side Effects of Antipsychotic Agents**

| | | | | | Controlled | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Author | Year | N | Age Range (years) | Medication | For Smoking | For Medications | For Oral Contraceptives | Results | Remarks |
| Chouinard and Annable (19) | 1982 | 40 | 18–65 | Pimozide, chlorpromazine | No | Yes[a] | No | Women had greater improvement | 4-week trial parallel design comparing pimozide with chlorpromazine; weights of men and women were equivalent |
| Simpson et al. (20) | 1990 | 9 | 23–43 | Fluphenazine decanoate | No | Yes[b] | No | Plasma levels higher in women | No significant difference in mg/kg dose by sex; small sample size and concurrent medication use may have influenced findings |
| Chouinard et al. (21) | 1986 | 40 | 18–60 | Fluspirilene, chlorpromazine | No | Yes[a] | Not known | Women needed significantly lower doses | Medication was titrated to response; no mention of oral contraceptive use |
| Ereshefsky et al. (22) | 1991 | 54 | —[c] | Thiothixene | Not known | Yes[b] | No | Women had higher levels | Many variables investigated; women were compared with men, but either group could have been receiving concurrent medications or smoking |
| Seeman (23) | 1983 | 101 | 20–? | Chlorpromazine equivalents | No | Not known | No | Women in their 20s and 30s required lower doses | Survey-type design did not allow authors to control for smoking and oral contraceptive use |
| D'Mello and McNeil (24) | 1990 | 112 | —[d] | Chlorpromazine equivalents | No | Yes[b] | No | Younger men and older women received higher doses | Retrospective review of uncontrolled treatment; amount prescribed may or may not have reflected amount required for response |
| Smith and Dunn (25) | 1979 | | | | | | | | |
| Study 1 | | 293 | 20–70 | Chlorpromazine equivalents | No | Yes | No | Severe dyskinesia more prevalent in women | Did not address differences among age groups |
| Study 2 | | 181 | 20–67 | Chlorpromazine equivalents | No | Yes | No | Older women and men had greater prevalence of severe dyskinesia | Analyses were recomputed by age and sex |
| Chouinard et al. (26) | 1979 | 261 | 19–67 | Chlorpromazine equivalents | No | Yes | No | Older patients more susceptible to tardive dyskinesia; younger men developed more severe form | Analyses were computed by age and sex |

[a] Procyclidine.
[b] Different drugs.
[c] Subjects were grouped into those 50 years old and younger and those older than 50 years.
[d] Subjects were grouped into those 40 years old and younger and those older than 40 years.

therapeutic dose for an individual may not be accurate. Further, estrogen has not been directly tested as an antipsychotic agent in humans; therefore, the binding capacity of estrogen may not be equivalent to antipsychotic efficacy. Thus, these studies do not confirm hypotheses about gender-related differences in therapeutic effect. However, several areas of further investigation are suggested by these findings. It is clear that age needs to be considered when looking at gender differences because of the critical interactions between gender and age. In addition, studies need to carefully define menstrual status, cycle phase, weight, and exogenous hormone administration in their subjects. Finally, it will be important to test some of the hypotheses regarding the psychotropic effects of ovarian hormones that are suggested by basic science research.

### *Benzodiazepines*

Whereas research on antipsychotic agents investigated possible gender-related variations in efficacy, research on benzodiazepines has looked more closely at pharmacokinetic issues (table 2). Few of these studies evaluated gender differences in therapeutic effects and

**TABLE 2. Literature Analyzing Gender Differences in Pharmacokinetics, Pharmacodynamics, and Side Effects of Benzodiazepines**

| | | | | | Controlled | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Author | Year | N | Age Range (years) | Medication | For Smoking | For Medications | For Oral Contraceptives | Results | Remarks |
| Greenblatt et al. (32) | 1980 | 44 | —[a] | Diazepam | Yes | No | Yes | Higher clearance of diazepam in younger women and in older women and men | Single intravenous dose; metabolites not assessed |
| MacLeod et al. (33) | 1979 | 19 | —[b] | Diazepam | Not known | No | Not known | Diazepam half-life in men significantly shorter | Single intravenous dose |
| Abernethy et al. (34) | 1982 | 16 | 29 (mean) | Diazepam | No | Yes[c] | Yes | Clearance of diazepam higher in oral contraceptive users than control subjects | Single intravenous dose |
| Giles et al. (35) | 1981 | 32 | 29 (mean) | Diazepam | Not known | Yes[d] | Yes | Clearance of diazepam lower in women using oral contraceptives than those not using oral contraceptives | Single intravenous dose |
| Ellinwood et al. (18) | 1983 | 18 | 21–26[e] | Diazepam | No | Yes[f] | Yes | Greatest impairment occurred on day 28 of menstrual cycle in women taking oral contraceptives and diazepam | No control group of women not taking oral contraceptives |
| Smith et al. (36) | 1983 | 30 | 20–78 | Triazolam, temazepam | No | No | Yes | With triazolam, lower clearance in elderly men; with temazepam, no gender differences in younger subjects but women had lower clearance than elderly men | Crossover study involving single oral doses |
| Greenblatt et al. (37) | 1980 | 36 | 22–84 | Oxazepam | Yes | Yes | Yes | Elimination half-life longer in women than in men; half-life not associated with age in men but tended to increase with age in women | Single-dose study; women weighed statistically significantly less than men |
| Jochemsen et al. (15) | 1982 | 36 | Not known | Nitrazepam | No | Yes[g] | Yes | Women taking contraceptives had higher steady-state levels than men and women not taking contraceptives | |
| Divoll et al. (38) | 1981 | 32 | 24–84 | Temazepam | Not known | None | Yes | Elimination half-life of temazepam longer in women than men | Single oral dose |

[a] Two groups, one with a mean age of 28 years and one with a mean age of 69 years.
[b] Two groups, one with a mean age of 26 years and one with a mean age of 82 years.
[c] Women were taking oral contraceptives.
[d] Control subjects were drug free; study subjects were taking oral contraceptives.
[e] Two groups, one of men and one of women, each with the same age range.
[f] Men were drug free; women were taking oral contraceptives.
[g] Men and half of the women were drug free. Half of the women were taking oral contraceptives.

side effects. Greenblatt et al. (32) found that diazepam, a benzodiazepine which is oxidatively metabolized, has a higher clearance in younger women than in men. The statistical significance of this difference disappeared in women who were 62–84 years old. MacLeod et al. (33) found that women metabolized the drug more slowly than men regardless of age (33).

Oral contraceptives have been found to decrease the clearance of benzodiazepines (34, 35). Ellinwood's group (18) postulated that oral contraceptives decrease the rate of absorption of diazepam, leading to a slower peak in levels. Cognitive and psychomotor tasks were more impaired during the week off hormones in women taking oral contraceptives because benzodiazepines peaked more quickly. This suggested that change in absorption rates for the week off hormones led to a dose of benzodiazepine which suddenly became intoxicating.

No sex differences in metabolism have been found for triazolam, a benzodiazepine that is also oxidatively metabolized (36). Nitrazepam, a drug metabolized by reduction, has not been found to have gender-related or menstrual-cycle-related differences in clearance (15). However, higher steady-state levels of this drug have been noted in oral contraceptive users (15).

Temazepam and oxazepam, benzodiazepines that undergo glucuronidation, had slower clearance rates among female subjects in several studies (36–38). This difference was apparent regardless of age (36). The methodology used in studies examining gender-related differences in the pharmacokinetics of benzodiazepines makes their generalizability provisional. The interindividual differences were large. In addition, researchers did not control for the enzyme-inducing effects of cigarette smoking (8) or autoinduction of enzymes over time, variables that could obscure or evoke sex-related differences. However, the preponderance of evidence suggests that benzodiazepines which are conjugatively metabolized have slower elimination rates in women than in men. Oral contraceptives seem to inhibit clearance and decrease the rate of absorption. Only one study looked at menstrual cycle effects (18), and it found no significant cyclic changes. Given the relationship between exogenous hormones and benzodiazepines, it would be worthwhile looking more closely for menstrual cycle effects. In addition to measuring plasma levels, it would be interesting to test physiological response throughout the menstrual cycle, as was done by Ellinwood et al. (18).

### *Antidepressant Agents*

Given the literature citing the higher prevalence of depressive disorders in women (39), the paucity of studies addressing sex-specific medication effects is surprising (table 3).

Hamilton et al. (40) investigated gender-specific neuropharmacological responses to antidepressant drugs. When men and women were treated with clorgyline, a negative correlation between changes in anxiety and activation was found for men but no such link existed for women. When amphetamine was administered, the negative correlation between antidepressant response and anxiety existed for both sexes, but only women showed a link between anxiety and depression.

A study by Davidson and Pelton (41) evaluated the efficacy of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) by gender in three types of atypical depression. Their data showed that depressed women with panic attacks had a more favorable response to MAOIs than to tricyclic antidepressants, whereas men who were depressed and had panic attacks responded more favorably to tricyclic antidepressants.

By reanalyzing data from an earlier study, Raskin (42) attempted to define gender-specific antidepressant effects. He found that young women (younger than age 40) responded less well to imipramine than did older men and women. Raskin hypothesized that the activating and energizing properties of imipramine exacerbated hostility in young women. Young men responded better to chlorpromazine, perhaps because of its sedating properties, but responded less well to phenelzine than younger women.

A study by Halbreich et al. (43) examined *d*-amphetamine-induced changes in mood and activation in postmenopausal women and young men. They found that postmenopausal women became dysphoric and sedated, but young men experienced euphoria and an increase in alertness with *d*-amphetamine treatment.

Little research has been undertaken examining differences in pharmacokinetics of antidepressants. Ziegler and Biggs (44) found no significant gender differences in plasma levels of amitriptyline and nortriptyline. Burrows et al. (45) had similar findings. Moody et al. (46) found that women had higher plasma levels of imipramine than men. In 1985 Preskorn and Mac (47) found that women and older subjects had higher plasma levels of amitriptyline than did young male subjects. These elevated levels in women may have occurred because these studies (46, 47) allowed co-administration of other medications, including oral contraceptives, which could affect tricyclic antidepressant plasma levels. Abernethy et al. (48) assessed concurrent use of imipramine and oral contraceptives and found that the latter inhibited hepatic metabolism of intravenous imipramine, resulting in lengthened half-life. When imipramine was given orally, this effect was counterbalanced by the change in oral availability and decreased apparent oral clearance. Not only does this illustrate the impact of co-administering oral contraceptives, it illustrates that mode of administration can potentially affect plasma levels differently in male and female subjects.

Finally, Greenblatt et al. (49) made important contributions to the investigation of sex differences in psychotropic agents by analyzing the pharmacokinetics of trazodone. They found that the volume of distribution was greater in women and the elderly, but clearance was significantly reduced only in older men.

### *Lithium*

Lithium carbonate has been the subject of several case reports suggesting menstrual cycle effects on serum levels. In at least two case reports (50, 51), lithium levels were found to be higher in the postmenstrual phase than in the premenstrual phase. Although this may have been attributable to increased water retention, this was not reported. However, a recent study of 14 women without bipolar disorder given lithium during follicular and luteal phases failed to show a difference between the mean lithium levels in the two phases (52). However, several individuals in this group did show a phasic difference. This illustrates that meaningful differences can be obscured by relying only on averages. Further, in this instance it would be important to look for phasic differences in women undergoing chronic lithium treatment. Since some women with mood swings complain of worsening during the late luteal phase of the menstrual cycle, it may be helpful to correlate lithium levels to symptoms throughout the menstrual cycle.

Adverse reactions to lithium may occur more frequently in women (53–55). Lithium-induced hypothyroidism predominates in women, just as thyroid disease is more common in women (56). Further, rapid-cycling bipolar illness, which some suggest is more prevalent in women (57), is associated with thyroid abnormalities (56). The importance of the hypothalamic-pituitary-adrenal (HPA) axis in women with affective illness is further suggested by studies of thyroid augmentation of antidepressant therapy; the potentiating effect may be largely confined to younger women (58).

## CONCLUSIONS

This paper has reviewed the theoretical basis for potential sex-related differences in pharmacokinetics and pharmacodynamic effects of psychotropic agents. A

**TABLE 3. Literature Analyzing Gender Differences in Pharmacokinetics, Pharmacodynamics, and Side Effects of Antidepressants and Mood Stabilizers**

| | | | | | Controlled | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Author | Year | N | Age Range (years) | Medication | For Smoking | For Medications | For Oral Contraceptives | Results | Remarks |
| Hamilton et al. (40) | 1984 | 36[a] | —[a] | Clorgyline, amphetamine[a] | Not known | Not known | Not known | Negative correlation between anxiety and clorgyline response for men; positive correlation between anxiety and amphetamine response in both men and women | Retrospective study with small sample |
| Davidson and Pelton (41) | 1986 | 190 | 41 (mean) | MAOIs or tricyclic antidepressants | Not known | Not known | Not known | Depressed women with panic had a more favorable response to MAOIs | Retrospective analysis of pooled data |
| Raskin (42) | 1974 | 880 | 16–70 | Chlorpromazine, imipramine, diazepam, phenelzine, placebo | Not known | Not known | Not known | Young women had less response to imipramine than older women and men; younger women had greater response to phenelzine and less response to chlorpromazine | Retrospective analysis; subjects did not necessarily have diagnosis of depression |
| Halbreich et al. (43) | 1981 | 14 | 24–62[b] | *d*-amphetamine | Not known | Not known | Not known | Postmenopausal women became dysphoric with amphetamine; young men experienced mood improvement | Two intravenous doses of *d*-amphetamine |
| Ziegler and Biggs (44) | 1977 | 65 | 40–69 | Amitriptyline, nortriptyline | Not known | Yes[c] | Yes | No gender differences in plasma levels | Small sample size; power analyses not included in results |
| Burrows et al. (45) | 1974 | 80 | —[d] | Nortriptyline | Not known | Yes[c] | Yes | No gender differences in plasma levels | |
| Moody et al. (46) | 1967 | 24 | Not known | Imipramine | Not known | No[e] | Not known | Nonsignificantly higher plasma levels in women | Small sample size and co-administration of other medications obscure results |
| Preskorn and Mac (47) | 1985 | 110 | 46 (mean) | Amitriptyline | Not known | No[e] | Not known | Women had higher plasma levels per mg of drug than men | Naturalistic study of inpatients |
| Abernethy et al. (48) | 1984 | 18 | —[f] | Imipramine | Yes | Yes[c] | Yes | Longer apparent half-life in patients taking oral contraceptives with oral administration of imipramine | Single intravenous dose |
| Greenblatt et al. (49) | 1987 | 43 | —[g] | Trazodone | Not known | Yes[c] | Yes | Reduced clearance in elderly men | |

[a] Two studies. For study 1, N=24; for study 2, N=12. For study 1, the mean age was 41 years; for study 2, the mean age was 33 years. For study 1, the medication was clorgyline; for study 2 the medication was amphetamine.

[b] Two groups, one of women aged 46–62 years and one of men aged 24–31 years.

[c] No other medication given.

[d] Two groups, one of men with a mean age of 43 years and one of women with a mean age of 38 years.

[e] Other medications were allowed.

[f] Two groups of women, one taking oral contraceptives (mean age=25 years) and a control group (mean age=29 years).

[g] Two groups, one with an age range of 18–40 years and one with an age range of 60–70 years.

major finding of our search through the literature on this topic is the paucity of experimental data directly addressing this issue. As intriguing as hypotheses about gender-based differences are, the interactions among body weight, fat distribution, hormone fluctuations, and the actual neuroanatomical substrates are very complex. Thus, findings from one drug may or may not be generalizable to other types of drugs or even to drugs in its own class. In our review of data-based articles, small sample sizes and confounding factors such as smoking and lack of attention to menstrual cycle phase complicate the findings. However, despite these limitations, there is evidence suggesting that there are gender-related variations. Some of the clearest findings include 1) the potential for women to have higher plasma levels of psychotropic drugs (especially when given with oral contraceptives) and 2) greater efficacy of antipsychotic agents and a greater likelihood of adverse reactions such as hypothyroidism and, in older women, tardive dyskinesia. These suggested sex-related differences clearly require more extensive investigation.

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# The Debate on Treating Individuals Incompetent for Execution

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*The question of whether to provide mental health treatment to prisoners under death sentence who have been judged incompetent for execution presents a powerful ethical dilemma for mental health professionals. Arguments that favor or oppose the provision of treatment are discussed in the context of the nature of the disorder to be treated, the type of treatment to be provided, the goals of treatment, and the relevant legal standard for determining competency for execution. Arguments against treating the incompetent include 1) the need to avoid harming those who are treated, 2) the risk that disclosures in therapy will be used for assessment purposes, 3) the need for paternalism when sufficient harm is necessary, 4) the adverse impact on the clinician, 5) the potential undermining of patient and public perceptions of mental health professionals, and 6) the poor allocation of limited resources. Arguments for treating the incompetent include 1) respect for the wishes of the prisoner, 2) the need to clarify the values underlying the refusal to treat, 3) the low risk of harm from some forms of treatment, and 4) the adverse impact on the milieu stemming from failure to treat. The authors conclude that treating incompetent prisoners may not violate ethical standards under some circumstances, and that some forms of treatment will require the informed consent of the prisoner.*

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In recent years, the issue of competency for execution has become a hotly debated clinical/legal question. This surge of interest has occurred despite the fact that this form of competency is based in common law and dates back to the thirteenth century (1–4). There appear to be at least two reasons for the renewal of the debate. First, the number of prisoners under death sentence in American jurisdictions has grown rapidly and, as of January 1991, exceeded 2,400 individuals (5). Second, the U.S. Supreme Court, in *Ford v. Wainwright* (6), held that executing the mentally incompetent would violate the Eighth Amendment prohibition against cruel and unusual punishment.

Currently, the issue of competency for execution has significantly more implications for mental health professionals than ever before. Firmly entrenched in statutory and common law and now with a constitutional basis, the concept of this form of competency is solidly established in our criminal justice system. Moreover, with the rapidly increasing population under death sentence, it seems inevitable that increasing numbers of mental health professionals will be asked to become involved in cases concerning an individual's competency to be executed. Even for clinicians who will never be involved with inmates under death sentence, the competency issue is useful as a heuristic device with which to explore issues such as trust and beneficence. The approach we take to weighing competing considerations and developing a position could also be used for situations in which the need for treatment competes with other demands, such as retribution and public safety.

There are two separate avenues to mental health professionals' involvement with inmates who have received the death sentence. The first is assessment, either before or after a formal finding of incompetency for execution. The second is the provision of mental health treatment for prisoners who have been found incompetent. The question of whether mental health professionals can ethically provide an assessment of competency for execution has been debated by many, including the present authors (3, 7–13). The parameters of how such assessment should be provided, if done at all, have also been discussed (12, and paper by S.L. Brodsky presented at the annual meeting of the American Psychological Association, Washington, D.C., 1986). The distinction between preadjudication and postadjudication assessment has been discussed; the latter presents ethical questions of even greater complexity (12).

The issue of treating a condemned inmate found incompetent for execution raises perhaps the most troubling questions, as the prisoner will have received a stay of execution pending restoration of competency. The

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primary focus of this article is on the ethical aspects of providing mental health treatment under such circumstances. (The constitutional questions raised by the issue of involuntary administration of one kind of treatment—antipsychotic medication—to prisoners who are incompetent for execution were before the U.S. Supreme Court in *Perry v. Louisiana* [14]. The Court remanded the case back to Louisiana for reconsideration in light of their holding in *Washington v. Harper* [15]. It is possible that the U.S. Supreme Court will eventually rule on the constitutionality of involuntary medication of prisoners incompetent for execution, but it appears unlikely to the attorneys involved in arguing the case [presentations by K. Nordyke and R.I. Salomon at the annual conference of the Forensic Mental Health Association of California, Pacific Grove, 1991]). While elsewhere we have argued that the best solution to these dilemmas is to commute the death sentences of incompetent inmates to life imprisonment (3, 12), here we focus on the ethical dilemma regarding treatment in cases in which commutations have not been made. One of our important points is that this is a powerful ethical dilemma because it occurs in the context of capital cases. "Death is different," an axiom that has long been recognized within the criminal justice system, will apply as well to the involvement of mental health professionals in this process.

Most states provide for transfer to some kind of secure psychiatric hospital for inmates found incompetent for execution (4, 16). For example, an inmate in Florida who is found incompetent for execution shall be "committed to a Department of Corrections mental health treatment facility" where "he shall be kept . . . until the facility administrator determines that he has been restored to sanity" (Florida Statutes, 922.07, subsections 3 and 4). Such a procedure is consistent with that recommended in the American Bar Association's *Criminal Justice Mental Health Standards* (17). One clear expectation in transferring an incompetent prisoner to a secure mental health facility is that the individual will receive mental health treatment. In this article we discuss whether and under what circumstances mental health treatment should be provided to such an individual, since one consequence of treatment may be restoration of competency and subsequent execution of the prisoner. (Because arguments about treating the incompetent for execution can be, in our view, closely bound up with feelings and values related to capital punishment, we offer the following statement of personal values, endorsed by each of us: we are not convinced by any existing data that capital punishment, as practiced historically or presently, actually deters crime [18]. We are convinced that the death penalty as currently applied has strong liabilities, including racial bias [19, 20], costliness [21], and the possibility of executing the innocent [22]. Our experience with death row inmates has led us to conclude that there are few individuals who, by their wanton disregard for human life, their willful and measured decision to kill, and their believable promises to kill again, have effectively given up their right to continue living. Unfortunately, our criminal justice system is not able to distinguish accurately between those who meet these criteria and those who do not. Nor does any conceivable incremental benefit of execution over life imprisonment seem to justify capital punishment in light of these difficulties. Thus, while we may debate the merits of the death penalty in theory, we are opposed to the way it is currently practiced. These values may affect the discussion that follows.)

## HISTORICAL BACKGROUND OF COMPETENCY FOR EXECUTION

Extensive discussions of the history of competency for execution are available elsewhere (1–4) and thus will not be detailed here. Some of the early justifications for excluding the incompetent from execution were religious (executing incompetent individuals does not allow those persons to put their spiritual affairs in order and prepare to "meet their Maker"), humane (madness is punishment in itself), and normative (executing severely disturbed individuals reflects badly upon society). More recent justifications for excluding the incompetent from execution have included the retributive aspect (individuals are not fully punished if, due to mental disturbance, they do not fully understand the implications of their death), the incompetent person's inability to assist counsel with last-minute appeals, and the psychological aspect (the individual cannot go through the "stages of dying" necessary for a humane death).

Empirically, the construct of competency for execution is important because the vast majority of individuals under death sentence are removed from death row for reasons other than execution. (From 1972 through December 1990, 143 prisoners were executed in the United States. During this same period, however, a total of 1,078 prisoners under death sentence were removed from death row for reasons other than execution: dismissal of indictment, reversal of judgment, commutation, resentencing, and natural death [5]). The capacity to work with counsel on collateral appeals is thus more important than it might seem.

Case law prior to 1986 had established that the "evolving standards of decency" of a civilized society forbade suffering beyond that which is "necessary . . . to extinguish life humanely" (23) under the provisions of the Eighth Amendment. In the more recent *Ford* decision (6), the Supreme Court held that executing the incompetent would, for several reasons, also violate the Eighth Amendment. The majority opinion questioned the retributive value of executing a person who does not understand the reasons for being executed. It described the abhorrence of killing a person who has "no capacity to come to grips with his own conscience or deity" and who experiences "fear and pain without comfort of understanding." Finally, the majority asserted that such executions would "simply offend humanity" and should be prohibited to "protect the dignity of society itself from the barbarity of exacting mindless vengeance." (Alvin Ford, still on death row in Florida and never having been judged incompetent for execution, died of natural causes on Feb. 28, 1991.)

## CONTEXT OF TREATING PERSONS INCOMPETENT FOR EXECUTION

Three broad positions on the involvement of mental health professionals in the treatment of individuals incompetent for execution have been described: always treat, sometimes treat, and never treat (7, 8). The first position (always treat) is held by clinicians who maintain that they are responsible for treating severe mental illness whenever possible, without regard for consequences. Severe psychosis is a painful condition which they cannot ethically refuse to treat when they are in a position to provide relief. Adopting such a position does not necessarily imply endorsement of capital punishment but, rather, separates the delivery of clinical services (which is in the realm of mental health professionals) from the administration of punishment (which lies within the domain of judges and corrections officials). It is also possible that the refusal to treat actually represents a concealed protest against the death penalty (13).

An intermediate position (sometimes treat) is taken by those who would provide treatment to individuals incompetent for execution, but only when the latter want to be treated. An important consideration for those holding this position is whether the benefits of treatment would outweigh the risks under such circumstances. This stance does, however, create another problem: it is quite possible that an individual who is incompetent for execution might also be incompetent to consent to treatment. Potential solutions to this dilemma may involve a "living will," allowing the prisoner (while competent) to express a preference regarding treatment if he or she should become incompetent for execution, or the use of a "next friend" to make the treatment decision (8, 24).

The third position (never treat) holds that the relief of suffering is not sufficient justification for providing treatment, as such treatment is provided with the goal of making possible the infliction of even greater harm. Would it not be more humane, such proponents ask, to allow someone to suffer with psychosis than to administer a treatment that might restore competency and terminate life? Several commentators have forcefully articulated this position (11, 25).

Each of these positions provides a valid perspective on the ethical dilemmas created by the prospect of treating persons incompetent for execution. However, none of the positions is very specific. Treatment is not defined; at times one author seems to mean psychotropic medication, while another may include both medication and psychotherapy. The nature of the disorders that might result in an adjudication of incompetency for execution is not specified. "Psychotic" is the most often cited description of such conditions; this may be both too vague and too narrow. The goals of treatment are insufficiently specified. Finally, the nature of competency itself is discussed globally rather than specifically. In the following discussion we address the ethical issues in these more specific aspects.

### *Relevant Disorders*

"Competency" is a legal term, not a medical or psychological term, so some translation is necessary. There appear to be three major classes of *DSM-III-R* disorders that might render an inmate incompetent for execution. Functional psychotic disorders such as the schizophrenias, mood disorders with psychotic features, delusional disorder, and psychotic disorders not elsewhere classified (schizoaffective disorder, schizophreniform disorder, and atypical psychosis) would constitute the first class. The second class would include certain organic mental disorders, such as delirium, dementia, amnestic disorder, organic delusional disorder, organic hallucinosis, and organic mood disorder, in which the symptoms are of a nature and severity sufficient to impair the individual's competency for execution. The third class would be mental retardation. It is noteworthy that previous commentators, in discussing "psychosis," were probably referring to the first class and parts of the second. Mental retardation has been addressed less frequently but is perhaps even more likely to yield cognitive deficits impairing competency for execution (26). While the mentally retarded may still be considered incompetent for execution if they meet state statutory requirements, the U.S. Supreme Court has made it clear that mental retardation in itself is insufficient to bar execution under the Eighth Amendment (27).

### *The Nature of Competency*

Any kind of legal competency implies tasks. The individual must be able to understand, know, believe, or do something related to the competency construct (28); there must be the ability to understand relevant concepts and act at a minimally acceptable level of skill on the basis of that understanding (29). In the case of competency for execution, the two most frequently cited elements within the standard are "understand" and "assist." The former refers to an individual's capacity to understand the nature of the death penalty and the reasons why this punishment is to be inflicted. The latter describes the capacity to assist legal counsel in ongoing appeals.

According to the *Criminal Justice Mental Health Standards* of the American Bar Association (17), the standard for competency for execution is that an individual should not be executed if "as a result of mental illness or mental retardation, the convict cannot understand the nature of the pending proceedings, what he or she was tried for, the reason for the punishment, or the nature of the punishment. A convict is also incompetent if, as a result of mental illness or mental retardation, the convict lacks sufficient capacity to recognize or understand any fact which might exist which would make the punishment unjust or unlawful, or lacks the ability to convey such information to counsel or the court" (p. 290). Of the 37 jurisdictions in the United States that have a death penalty and a relevant law relating to competency for execution, only two have standards that conform to the "understand" element, and another eight have "understand and assist" standards. Two states define competency for execution in terms of "mentally ill and need for treatment"; the remaining states use only a brief, unelaborated definition (e.g., "insane," "incompetent," "unfit") (16). The U.S. Supreme Court had the opportunity in the *Ford* case (6) to provide a single standard for this competency, as it had done for competency to stand trial (30). It did not do so, although Justice Powell, in his concurring opinion, did conclude that the test of incompetency for execution should be whether the prisoner is aware of his or her impending execution and of the reason for it. As a result of the failure to define a standard for competency in the *Ford* majority opinion and the lack of specificity in their pre-*Ford* statutes, most states do not provide specific guidance regarding the necessary tasks for determining competency for execution. The states that offer more explicit guidelines differ about what these are.

In an effort to help construct a consensual definition of competency for execution, we offer the following three tasks as potential components: 1) understanding the nature of capital punishment and the reasons for its imposition, 2) assisting counsel in ongoing collateral appeals, and 3) spiritually and psychologically preparing for death. While the latter does not appear in any of the statutes or case law, it has been proposed (31). We include it because clinicians need to address all possible dimensions unless or until the definition of incompetency is restricted by appellate courts.

### *Treatment and Treatment Goals*

The types of mental health treatment that might be provided to prisoners incompetent for execution also need further specification. Psychotropic medication is one such treatment, but we will refer to two other types as well. The first is psychotherapy; the second involves a combination of education, skills training, and behavioral therapy that might best be described as psychiatric rehabilitation (32, 33).

Such treatments might be delivered with a number of goals in mind. In any forensic setting, a primary purpose of treatment involves assisting an incompetent patient to regain legal competency. Some would argue that competency for execution is no exception and that a major reason for treating such an individual would involve promoting the recovery of competency. This treatment might be indirect (e.g., removing a disability, such as an actively psychotic condition, and thereby allowing the capacities to perform competency tasks to reemerge) or direct (e.g., enhancing the capacity to interact effectively with counsel through communication skills training). There are, however, other goals that therapists could pursue as well. These include relief of suffering brought on by a psychotic condition, provision of comfort and support and the opportunity for catharsis, enhancement of the individual's capacity to fight effectively for legal rights, and provision of an opportunity to prepare psychologically for death. While the last two goals may arguably relate to the individual's competency status in some jurisdictions, the first two are largely situation-independent treatment goals.

## ARGUMENTS AGAINST TREATING THE INCOMPETENT

### *First, Do No Harm*

The notion that psychiatrists and psychologists providing treatment should not harm patients is probably more of an implicit understanding than an explicit ethical canon of either profession. *Primum non nocere* (first, do no harm) is a long-established tenet of the medical profession, although it is no longer a part of the American Psychiatric Association's *Principles of Medical Ethics* (3, 34). Psychologists are ethically obligated to "protect the welfare of the people and groups with whom they work" (35, 36). This sets a similar tone, and the ethical issue here is the same for psychiatrists and psychologists. Mental health professionals are helpers, with a primary obligation to assist and not harm those who receive their services.

### *Risk That Disclosures in Therapy Will Be Used for Assessment Purposes*

The establishment of an effective treatment relationship depends on whether the individual receiving treatment can trust the professional who is rendering it. This would seem particularly true for psychotherapy with persons who are incompetent for execution. Being under death sentence can have a powerful polarizing effect on a prisoner's perceptions: others are seen as either friends or enemies. There is thus the temptation to view the therapist in one of these two roles. It is not clear whether the prisoner can be accurately informed that information provided in therapy will not be disclosed except in instances involving an increased risk of violence by the patient toward another individual or himself or instances of escape. There is the very real possibility that psychotherapy with a prisoner who is incompetent for execution could result in the use of confidential disclosures for the purpose of assessing the person's competency for execution. In many inpatient settings, disclosures made during therapy are shared within a "circle of confidentiality" that may include supervisors in the chain of clinical responsibility, social workers, nurses, and other treatment team members (37). The risk that disclosures made during therapy will be used for assessing competency for execution is particularly acute under this model and when there is not a strict separation between treatment and assessment functions (3, 12).

### *Paternalism Is Necessary When Significant Harm Is Possible*

There are times when it is necessary to decide that the potential risks of treatment sufficiently outweigh the benefits, so that treatment should be withheld whatever the wishes of the patient or the external demands. Surely, the treatment of those incompetent for execution must be among such cases. Psychotropic medication, which may have an immediate impact on the symptoms rendering an individual incompetent for execution, is the best example. The physician must weigh the potential gain from this form of intervention against the risk that the individual will quickly have a remission of symptoms, regain competency, and be executed.

There is certainly the possibility that an individual who is incompetent for execution might also be incompetent to consent to psychotropic medication (7). This must be considered in any decision to prescribe medication. While the legal right to refuse medication may be limited in prison (14, 15), there are also ethical considerations confronting a physician under these circumstances. Given the potential consequences that could follow a medication-induced improvement in mental condition, the ethics-induced demand for the necessary level of competency to consent to this particular treatment should be very stringent.

### *Adverse Impact on the Clinician*

A clinician attempting to administer any kind of treatment to an individual who is incompetent for execution can experience powerful feelings of confusion, anger, and ambivalence. The awareness that the application of one's craft may result in the death of another human being, even indirectly, creates a situation in which a clinician can feel strong pulls in two directions. On one hand, it is very difficult to be in proximity to someone who is suffering from a mental disturbance, and who may even be asking for help, and not render help. Such a decision, in our experience, is far easier to make in the abstract than in the clinical situation. On the other hand, the awareness that death could ensue soon after treatment is enough to give almost any clinician pause. This conflict is exacerbated by personal contact with the inmate.

In one recent instance, the feelings of clinicians were described in these terms, and they unanimously voted against repeating the entire process, having failed "by bitter experience" to resolve the difficult emotional dilemma created by this situation (25). (The dilemma has never been resolved. The prisoner was transferred from the forensic service at Florida State Hospital to the Corrections Mental Health Institution in 1985 as a result of a change in state statute. After having been evaluated by the Corrections Mental Health Institution treatment team, he was returned to Florida State Prison 2 years later. The team did not express a clear opinion with regard to the prisoner's competency for execution. They did state that he apparently understood the nature of his legal situation at the time of the report—although given the nature of his mental illness, it would be hard to tell on any given day in the future whether he would understand—and had also obtained maximum benefit from treatment. Following his transfer to Florida State Prison, the prisoner refused to cooperate when a new team of three psychiatrists attempted to assess his competency for execution. The stay of execution that had been granted because of his incompetency was therefore vacated by the governor. The prisoner remained on death row as of February 1992.) There have been no other cases in which an individual has been judged incompetent for execution. However, the emotional impact upon clinicians from this single case provides an ominous foreboding of things to come.

### *Undermining Patient and Public Perceptions of Mental Health Professionals*

The professions of medicine and psychology are multifaceted. Both include scientific, professional, and public policy components. However, the facet involving direct patient services is arguably the most visible and the most prominent in the public eye. Actions that run counter to the "healing profession" image may thus have a disproportionately large impact on these professions as a whole. There can be little doubt that there will be widespread dissemination of information about the actions of psychiatrists and psychologists in cases of incompetency for execution. The avid public interest in death penalty cases, fueled by intense media scrutiny, is a potentially volatile situation. The spectacle of the smiling, white-coated doctor, syringe in one hand and hangman's noose in the other, may be quickly dismissed as outrageous hyperbole—until it appears in a national magazine (38) or on the editorial page of a prominent newspaper.

### *Poor Allocation of Limited Resources*

The supply of mental health professionals is far outstripped by the demand, particularly from forensic and correctional facilities (39, 40). Treatment (of whatever form) provided to an inmate who is incompetent for execution can be extremely time-consuming. Because of the high visibility of the case, intense media interest, heightened concern for security, other institutional concerns, ethical issues, and personal reactions of the clinician, such a case can require more clinical resources than even presentencing capital punishment cases of comparably high visibility. Treating prisoners incompetent for execution is simply a poor way to spend valuable resources, from an individual clinical standpoint, from a psychiatric institutional standpoint, and as a matter of public policy.

## ARGUMENTS FOR TREATING THE INCOMPETENT

### *Respect for the Wishes of the Prisoner*

The strongest argument for treating persons incompetent for execution is that they have a right to such treatment if they want it. "Informed consent" followed by delivery of mental health service is an ethical cornerstone of both psychiatry (34) and psychology (36) that arguably applies in many forensic contexts (41, 42). A situation analogous to the treatment of incompetent prisoners involves the ongoing legal appeal process following a death sentence. There are some prisoners who wish to discontinue collateral appeals, presenting a similar dilemma for the attorney: abiding by the expressed wish of the client may hasten his or her death, yet there is a compelling argument that this respect for the client's wishes actually enhances the dignity and humanity of the client (8, 24).

The question of whether consent to mental health treatment under these circumstances can be validly given is clearly a difficult one. In the civil commitment context, there are three essential elements to determining the validity of consent to treatment: disclosure, competency, and voluntariness (43, 44). It may well be that competency to consent to such treatment could always be questioned under such circumstances (45) and that such competency should be assessed broadly and include both the rationality and informed nature of the decision (10). Thus, a large percentage of prisoners who are incompetent for execution might also be incompetent to consent to treatment. However, if it can be assumed that valid consent to some forms of treatment can be obtained in some cases of incompetency for execution, then we are left with a clearly stated, competently given preference to receive treatment.

There are also other ways in which competent consent might be obtained: 1) from the prisoner before the incompetency issue is ever raised (comparable to the living will), 2) from the prisoner after a brief trial of medication designed to restore competency to consent, and 3) from a "next friend" appointed by the court. (Keith Nordyke, the attorney representing Michael Perry in *Perry v. Louisiana* [14], filed a motion for his own appointment as Perry's "next friend" for the purpose of deciding about the administration of psychotropic medication. This motion was granted by the trial court, and Perry's medication was stopped when Nordyke refused permission for its administration. The trial court removed this decision-making authority from Nordyke after 6 months. This points to a practical difficulty in applying the "next friend" concept: a trial judge inclined toward or against the death penalty can greatly influence the medication decision by appointing a "next friend" who is similarly inclined.) When competent consent can be obtained, by whatever means, it seems reasonably clear that any subsequent refusal to treat would be simply a substitution of the clinician's values for those of the prisoner.

### *Confusion of Values*

The second argument for providing treatment is based on the notions that 1) refusing to treat is a veiled protest against the death penalty and 2) the principles of beneficence (doing good) and nonmaleficence (doing no harm), so clearly important in nonforensic treatment situations, are far less applicable in a forensic treatment context. The first point has been made by Mossman (13), who gives the example of a mentally disordered convicted murderer serving a life sentence who is subsequently transferred to a mental hospital. Few mental health professionals would have qualms about providing treatment under those circumstances, although it might "bring about" punishment by returning the individual to prison. A comparable example might be that of individuals who are charged with first-degree or life-sentence felonies but are incompetent to stand trial on these charges. To our knowledge, nobody has cited ethical difficulties in treating under these circumstances, even though treatment might again facilitate the administration of punishment through restoration of competency to stand trial.

Since it is not the administration of punishment per se but rather the punishment by death that creates the ethical difficulties, this argument concludes that such difficulties are really a protest against the death penalty under the guise of professional ethics, a conclusion also reached by Bonnie (9). While there is no doubt that mental health professionals should, like any other citizens, be free to express their opposition to capital punishment, some would argue that such opposition should be presented in an intellectually honest way: openly and in their roles as citizens rather than as professionals.

Further, a strong argument has been made that the principles of beneficence and nonmaleficence are not central to forensic ethics (46). When there is not a promise that such principles will govern the relationship, as in cases of evaluation for the purpose of court testimony to advance the general interests of justice, then they arguably do not attain primacy. While Appelbaum (46) draws a distinction between forensic and treatment procedures, it is not clear whether treatment for the purpose of regaining a prisoner's criminal competency is serving the needs of the state (by advancing the general interests of justice) or of the individual (by diminishing suffering). It can be argued that it is largely the needs of the state which should be addressed in the context of competency for execution and that treatment decisions should not be made solely on the basis of the interests and needs of the incompetent prisoner.

### *Some Forms of Treatment Have Low Risk of Harm*

Much of the discussion about treating persons incompetent for execution seems to assume a strong causal connection between treatment and regaining competency. This assumption may not be accurate, at least for some forms of treatment. The clearest connection between treatment and psychotic symptoms occurs in regard to antipsychotic and mood-stabilizing medications. In cases of schizophrenia, affective disorders, and organic mental disorders with psychotic symptoms, the prescription of appropriate medications can directly ameliorate symptoms such as perceptual disturbances, severe communication disturbances stemming from formal thought disorder, and disturbances in thought content, such as delusions. These kinds of symptoms in turn may have a direct impact on an individual's ability to understand the nature of death and the reason it is being inflicted upon him or her. Within the broader view of competency for execution, such symptoms could also have an adverse impact upon an individual's ability to work productively with counsel on collateral appeals and could impair the capacity to prepare for death. On the other hand, medication would not have an effect on the cognitive deficits stemming solely from mental retardation.

Other forms of treatment may present a different picture. The evidence shows that psychotherapy or counseling alone, in the absence of other forms of treatment, is not effective in alleviating the biologically based "positive" symptoms of schizophrenia, affective disorders, and organic mental disorders (47). Psychotherapy could therefore be delivered to an individual found incompetent for execution with the assumption that the risk of harm stemming from improvement would be low. The comfort, catharsis, and support from such psychotherapy would be valuable, and the therapist might assist the individual in preparing for death with as much dignity and humanity as possible under the circumstances, if this were not part of the competency criteria.

Psychosocial rehabilitation involves teaching a mentally ill patient the additional skills to permit him or her to behave and interact in a relatively nonpathological manner, despite the continued existence of the underlying illness (48). The connection between this kind of treatment and competency-relevant behavior seems potentially strong. In effect, one might be teaching an individual to behave "as if" he or she understood the nature of the death penalty and the reasons for its being administered. One might also be teaching the individual to communicate more effectively, which could improve the ability to interact with counsel. Other skills, however, such as stress management techniques, could theoretically improve the person's coping ability without having a direct effect on competency-relevant capacities. It therefore makes a difference which skills are taught and which deficits are to be remediated. Clinicians could conceivably deliver certain kinds of psychosocial treatment to individuals incompetent for execution without the concern that such treatment would immediately make it more likely that competency would be regained.

### *Adverse Impact of Failure to Treat on the Milieu*

Since most states provide for the transfer of an incompetent prisoner to a high-security mental health institution (16), we must consider the impact of selective refusal to treat certain patients within such facilities. What will happen to incompetent prisoners who are not treated in any way? Will they be confined to their rooms and ignored by the staff? Will they interact with the direct care staff but not the treatment staff? What impact would such selective treatment refusal have on the other patients and on the therapeutic milieu? It seems likely that it would increase the sense of isolation and estrangement of incompetent prisoners and exacerbate the confusion and mistrust of the staff that may already be exhibited by acutely disturbed patients in an inpatient setting. Both kinds of effects are antithetical to the goals of an effective inpatient milieu: to increase patients' sense of security and interpersonal trust and diminish their isolation and confusion. To the extent that the therapeutic milieu is an important element in the effectiveness of inpatient treatment, the selective refusal to treat one patient could damage the treatment prospects for more than that single individual.

## SYNTHESIS

The arguments presented in this article primarily encompass the ethical and moral considerations relevant to treating persons incompetent for execution. Legal considerations have been relatively less emphasized; while they are neither mutually exclusive of nor synonymous with ethical concerns, it is possible to envision a constitutional analysis that reaches a different set of conclusions.

Despite this caveat, however, the arguments we have presented help clarify the ethical issues involved in the provision of mental health treatment to prisoners who are incompetent for execution. The decision about whether to provide such treatment should depend on the nature of the treatment to be provided, the goals of treatment, the standard for competency for execution, and determination of the prisoner's ability and willingness to consent to the treatment.

Specificity is important because one of the major objections to providing treatment concerns the possibility that a treated individual will be put to death if the treatment is successful. Some kinds of treatment have a low causal connection with improvement in competency-relevant capabilities but may nevertheless "help" under some circumstances. Psychotherapy or counseling is the class of mental health treatment for which there is the lowest causal connection between treatment and competency-relevant behavior. Certain kinds of psychosocial education interventions—in the area of stress management, for example—are also unlikely to affect an individual's ability to understand or assist in relevant ways. Cognitive deficits experienced by the mentally retarded are unlikely to be altered with either medication or therapy, although perhaps the relevant understanding could be improved through certain kinds of training.

On the other hand, the administration of antipsychotic or mood-stabilizing medications is much more likely to effect a change in the competency-relevant thinking and behavior of individuals with schizophrenia, organic mental disorders with psychotic features, and affective disorders with psychotic features. It is in these cases that the importance of informed consent to treatment becomes paramount. The importance of obtaining consent—informed, voluntary, and competent—thus varies according to the kind of treatment being considered. For treatments having a strong therapeutic link to competency-relevant symptoms (e.g., psychotropic medications) and thus presenting a high risk to the prisoner, there appears to be an ethical demand to obtain informed consent prior to delivery of treatment. For other forms of treatment (e.g., milieu, psychotherapy) having a weaker link to competency-relevant symptoms but potentially providing other benefits (e.g., support, catharsis, contributing to the broader milieu), the demand for fully informed consent seems less compelling, and the threshold for consent should be lower.

Even with medication, however, if informed consent can be obtained, then there is an argument for providing the treatment requested by the patient. Respect for the prisoner's autonomy versus the need for paternalism under compelling circumstances are the considerations that must be weighed against each other. A legal analogy would be the predominant position of the courts regarding the insanity defense for defendants who refuse to invoke it when it would be worthwhile. Until recent years, in order to preserve the "moral integrity" of the law, this defense was interposed by the court against the defendant's wishes (for example, *Whalem v. United States* [49], in which the Circuit Court of Appeals for the District of Columbia appeared to establish a duty for trial judges to impose an insanity defense when it would be likely to succeed, regardless of the defendant's wishes.) Now, however, the prevailing view seems to involve honoring the decision of a competent defendant to avoid using this defense (8, 44, and several post-*Whalem* decisions by the U.S. Supreme Court, including *North Carolina v. Alford* [50] and *Faretta v. California* [51], and by the District of Columbia Court of Appeals in *Frendak v. United States* [52]).

It is crucial, however, to verify that consent is indeed valid under circumstances of competency for execution. It is possible that an incompetent prisoner might be treated with medication only to the point that he or she is able to make a competent decision about further treatment, although this would increase the risk of alleviating competency-relevant symptoms. It is possible to assume that an individual who is both incompetent for execution and incompetent to consent to treatment would not, if competent, give consent to be treated. The preferable course here would seem to involve having a "next friend" (a role played by a relative or advocate rather than the defense attorney or mental health professional) weigh these possibilities in order to make a substituted judgment. It has been argued that there is probably no legal right for a prisoner to refuse treatment under these circumstances (8), a position that is consistent with the U.S. Supreme Court's recent decision in *Washington v. Harper* (15). However, we would conclude that there is an *ethical* demand for mental health professionals to abstain from the involuntary treatment of someone who is incompetent for execution, at least with treatments likely to alleviate competency-relevant symptoms. On the other hand, it would not appear unethical to integrate an incompetent inmate into a therapeutic milieu, even without the prisoner's consent, because of the potential benefits to the prisoner and the other patients and the relatively low risk of "harm."

The atmosphere surrounding the death penalty is powerfully charged. One's position on capital punishment can play a large role in determining whether to treat individuals who are incompetent for execution. Reluctance to provide any kind of treatment can be a veiled protest against the death penalty, although not necessarily against punishment itself. "Above all, do no harm" is not necessarily a relevant principle for treating individuals in the criminal justice system, if one includes criminal sanctions under "harm." There are two reasons why this dictum is not applicable. It does not offer a distinction between evaluations of competency for execution and presentencing evaluations, and it would also condemn other kinds of clinical evaluation in the postsentencing phase of the criminal justice system that have never been seen as problematic by those who accept any kind of clinical forensic involvement in the criminal justice system (8). However, the close temporal proximity to drastic harm, even if it is an indirect rather than a direct consequence of treatment, can create intense difficulty in the treatment of persons who are incompetent for execution. This is the mental health variant of considering punishment by death as "different," something that has been recognized within the criminal justice system for some time (8, 53).

The entire question of treatment for persons incompetent for execution presents a "lose-lose" situation for mental health professionals. It is difficult to abstain from treating a person in need. It is equally difficult to provide treatment to an individual under these circumstances. The personal consequences are also difficult. In addition, the potential loss of public esteem for the profession, stemming from the public's perception that treatment professionals are closely involved with capital punishment, may be a powerful consideration.

## CONCLUSIONS

One of the recommendations made elsewhere (12) is that mental health professionals should consider very carefully the decision about whether to participate in the assessment of competency for execution. This recommendation seems equally apt for the decision about providing treatment. Clinicians should carefully weigh any decision to participate under these circumstances. However, it also seems appropriate to conclude that such a decision should be made on an individual basis rather than as a profession. We have argued that any decision about treating persons incompetent for execution should involve a variety of considerations. A blanket recommendation against participation does not seem indicated on ethical grounds.

There are, however, some unresolved questions about how to participate that might be usefully addressed by the professional psychiatric and psychological associations. To what extent is treatment of incompetent prisoners a clinical situation, emphasizing the principles of beneficence and nonmaleficence, and to what extent is it a forensic situation, in which the needs of society may be weighed more heavily than those of the individual? Clearer answers may await our professions' responses to Appelbaum's call (46) for the development of a comprehensive set of forensic ethical standards.

Competency for execution presents a very complex set of ethical and moral problems for mental health professionals involved with these cases. The discussion in this article leads us to conclude that there is no single, ethically proper position on the treatment of persons found incompetent for execution. It appears unethical to administer against the prisoner's wishes treatment that is highly relevant to competency, such as antipsychotic medication for psychotic disorders. It may not be unethical if the prisoner consents to receiving such medication, although there are problems in determining what constitutes "consent." If the treatment is unlikely to affect competency-relevant symptoms, however, then it is not unethical to provide it. Finally, the circumstances of each case will influence some of the treatment decisions for which there are no clear ethical mandates. We hope that these conclusions, and the discussion on which they are based, will introduce more shades of gray into a debate that has often been treated in black and white.

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# An Overview of Sport Psychiatry

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Objective: *Although the application of psychiatric methods and principles to sports is relatively unsystematic at this time, athletic behavior presents several issues of interest to psychiatry. The aim of this paper is to provide a framework for understanding the developmental, occupational, pathologic, therapeutic, and research aspects of sport psychiatry.* Method: *Studies in psychiatry, psychology, and psychoanalysis provide the basis for this overview, and nonscientific works are cited where they illuminate various issues. Illustrative case examples are also reported.* Results: *It is proposed, but not proven, that athletes undergo phase-specific development and that they may suffer impairments in adapting to the athletic context. This context may also modify treatment modalities.* Conclusions: *There is a need for more clinical studies of athletes, especially in the realms of childhood traumas, competitive issues, and mental illnesses. Because of the close relationship of mental and physical phenomena in sports and because athletic behaviors are often precisely measurable, athletics may constitute a fruitful area for psychiatric research.*

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In the 1920s, an educational psychologist at the University of Illinois, Coleman Griffith, first applied the principles of psychology to sports (1). His work stood alone for several decades, until sport psychology was again taken up by Ogilvie (2) and others (3–5). Today, sport psychology is a comprehensive discipline, with journals (*Journal of Sport and Exercise Psychology, International Journal of Sport Psychology*), graduate programs (6), national and international societies (7), and numerous textbooks (8–10).

Compared to psychology, psychiatry has so far devoted rather little attention to sports. Beisser's pioneering case studies of athletes in therapy (11), published in 1967, raised interesting questions regarding the psychotherapy of athletes and the impact of athletics on the personality. Arnstein (12), in 1976, discussed some of the emotional problems of adolescent athletes. More recently, psychiatrists have published work on such topics as clinical guidelines (13), the conceptual underpinnings of sport psychiatry (14), obligatory running (15), and the psychiatric effects of anabolic steroid use by athletes (16, 17). These papers are few, however, and while they highlight several psychiatric issues in sports, they do not constitute a systematic body of knowledge.

One related area receiving greater attention by psychiatrists is the use of exercise as a therapy for anxiety and mood disorders (18–20). Both individual case studies (21) and efficacy trials (20) have been reported. However, according to Morgan (22, 23), who has reviewed this work, the therapeutic benefits of exercise cannot as yet be claimed with certainty. Altshul (24) came to the same conclusion on clinical grounds. In any case, exercise therapy for psychiatric disorders does not represent an application of psychiatric methods to the field of sports per se, so in this respect it is peripheral to the field of sport psychiatry. As Massimino said, "The primary role of the sport psychiatrist must be a clinical one: to prevent, diagnose, and treat the psychiatrically related medical issues confronting the athlete" (13, p. 56).

In principle, psychiatry may contribute to sport medicine. Ours is a science that studies mind-body relationships. Our biopsychosocial perspective may lend itself to the study of such problems as recovery from injury, healthy and unhealthy aspects of competition, the relationships between psychological functioning and athletic performance, and the effects of athletic activity on neuroendocrine function.

For example, several studies (25, 26) have shown a significant correlation between life stress and the frequency of athletic injury. In one report (27), the personality characteristics of hysteria and hypochondriasis, as measured by the MMPI, adversely affected recovery from knee surgery. The role of parental influence in the genesis of competition anxiety in children participating in sports has also been pointed out (28–30). The behavioral, analgesic, and cardiovascular effects of exercise have been linked with

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endogenous opioid systems in rats (31), and in humans the calming effect of aerobic training may be reversed by naloxone (32). The cognitive variable of field dependence/independence has been related to performance in basketball players (33). All of these findings are suitable for further study from a psychiatric perspective.

In the last decade, psychiatric involvement in sports appears to have grown. Faced with drug abuse, professional sports has sometimes sought the help of psychiatrists (34). Psychiatrists have also been called on to facilitate performance (13). The American Academy of Sports Physicians has established a sport psychiatry committee, and one medical school has set up a formal program in the field within its department of psychiatry (35). These are appropriate developments for sport medicine, especially since the services of sport psychology are often administered by practitioners with little or no clinical training (36).

In this overview I attempt to integrate the findings and ideas of various observers of sports with the basic principles of clinical psychiatry. Although sport psychiatry is in its infancy, this heuristic attempt to define its boundaries is meant to facilitate and encourage further work in the field.

## DEVELOPMENTAL PERSPECTIVE

The epigenetic theorem of behavioral science states that the capacities of the human being unfold in a sequence of stages, each stage building on the preceding ones and providing a foundation for the stages that follow. This theorem has been elaborated by Freud, for libidinal development (37); Erikson, for identity formation (38); Piaget, for cognition (39); and Lidz, for personhood (40). For athletic development, similar epigenetic schemes have been proposed (14, 28). Although these schemes are preliminary constructs with little empirical validation, they aim to place athletic activity within the context of normal human development.

A hypothetical first stage, from birth to approximately age 3 years, is thought of as the age of emergent body narcissism, in which the future athlete discovers the body's potential as an instrument of pleasure, experiment, and discovery (14, 28). Children's spontaneous motor behavior, as well as the enjoyment of such passive activities as swinging, inversion, and the like, promote an appreciation of physical play (28). Although children may imitate aspects of sporting behavior before age 3, they do not yet understand the rules of society's games (28).

A hypothetical second stage, corresponding to the Oedipal years, is thought to be important for the emergence of competitive strivings (14). The pre-Oedipal child's struggles of will evolve toward an interest in competition for its own sake. Although at this age children enjoy beating opponents in quasiathletic contests, they may not as yet be concerned with winning as it is defined in true sports, as the following example illustrates.

*Case 1.* A group of 4- and 5-year-olds ran a 50-meter race. One child, running faster than the others, looked behind her for a rival. She slowed down to allow the rival to catch up to her, whereupon she resumed running fast and pulled ahead. She then looked for another opponent, and then another. In this way, moving side to side as well as forward and back, she achieved several victories in a single race. Although she came in second by standard measures, this did not appear to dampen her satisfaction.

In a third stage of athletic development, corresponding to the latency years, children spontaneously organize their own athletic contests (14). The progress in athletics during latency is thought to depend on cognitive maturation (14), specifically the development of concrete operations (39), which enable the child to understand such notions as position, follow-through, and generalized rules (14).

For example, to run past a finish line, rather than stop just at the line, as preoperational children tend to do, children must possess a notion of "reversibility" and understand that their actions after a race is over affect the outcome of the race itself (14). Similarly, achieving a notion of "conservation" (39) enables latency-age soccer players to maintain position, rather than swarm to the ball, as preoperational children often do.

On the whole, latency is thought to be a crucial time for the athlete's learning about how things work, including basic techniques, rules, and social roles (28). Latency has therefore been termed the age of "playground conditioning" (14). Because it is the age in which children first understand true sports, it is the age that is most studied in the field of youth sports (10, 41, 42).

During the next hypothetical stage of development, adolescence, athletics become imbued with passion and idealism (14, 28). Although preadolescents are happy about winning and disappointed about losing, they may not yet experience the emotional upheavals of teenage athletes (12). In particular, sexuality and self-esteem become especially important for athletes in adolescence (12).

The development of body narcissism, competitive strivings, playground conditioning, and passion and idealism prepare the person for athletic maturity (14). For those who reach this final stage, athletic training appears to become more systematic and creative than it had been before (14).

These hypothetical stages await experimental verification, but they help us to understand certain frequently noted problems in youth sports. Martens (43), Lewthwaite and Scanlan (29), and others (28, 42) have called attention to the potential of sports for generating unwelcome anxiety in young people. Often this is said to result from inappropriate adult behavior. From a developmental perspective, this behavior may represent a premature insistence on athletic attitudes for which the child is not yet ready. Latency-age children may be expected to summon the fervor of adolescence. Five-year-olds may be subjected to mature training methods. The following case illustrates that attitudes appropriate to athletes in adolescence may be encouraged in children as young as 3.

*Case 2.* Although Max, a football coach, was a basically gentle man, he continually urged his players to display a "killer instinct." Max frequently brought his son Benjy, who had just turned 3, to practice. Although the child ran and played freely with various people at the field, he never smiled and always maintained an expressionless face.

At home with his family, Max played with his son after dinner. As he did with his players, Max persistently urged Benjy to "look mean" and modeled an angry face. The child appeared confused by the command, but after several tries adopted a distorted look that was part grimace, part fright. He appeared confused about the expressive functions of his facial muscles.

The developmental perspective may also help us to think about the impact of adults' increasing organization of youth sports. In the last 25 years there has been a major shift in athletic settings for children, from self-organized playground games to leagues organized by adults (44). Although youth sport leagues provide many opportunities for youngsters and their families to participate, spontaneous games provide opportunities of a special kind.

We know the importance of latency for socialization processes (40). In their spontaneous games, youngsters experiment with solutions to such problems as how to deal with winning and losing, how to adapt to a displacement in the social hierarchy, and how to resolve conflict. When play is disrupted by a heated dispute over the rules—for example, whether or not a given action constitutes a foul—it may be unwise for an adult to quickly resolve the matter in the interest of resuming play. As Piaget explained in his study of morality (45), for which he used as subjects children playing marbles, in disputing the rules the contestants are constructing them by refining and comparing their personal notions with the notions of their peers. The problem of how to preserve spontaneity and opportunities for psychological growth within organized youth sport leagues is one that sport psychiatry might well consider.

## PSYCHODYNAMIC FACTORS IN SPORTS-RELATED PROBLEMS

Although sport psychiatry is too young for a formal nosology, the sports-related problems that have been identified may be divided into five categories. These are 1) sudden performance failure ("choking") (46, 47), 2) prolonged performance failure (slump) (48), 3) emotional factors that contribute to injury (25, 26) or prolong recovery from injury (27), 4) interpersonal problems with coaches and teammates (2), and 5) training problems of various kinds, including those relating to retirement (11, 49).

This division is one of convenience, and there seems to be a degree of overlap. For example, Nicholi (50) reported how interpersonal problems can prolong the poor performance of a team, and Ogilvie and Tutko (2) observed that a "choking" athlete may come in conflict with a coach. A severe injury may bring retirement issues to the fore (51). Since there have been no epidemiologic studies of these problems, it is impossible to say how prevalent they are among athletes.

Mahl (52) elucidated the role of psychological conflict and defense in the genesis of a wide variety of behaviors. The person in conflict "is prompted simultaneously by incompatible response tendencies" (52, p. 20). The various defenses result in "avoiding or decreasing the aversive motivational state" and "avoiding or mitigating a perceived or anticipated danger situation" (52, p. 40). Ogilvie and Tutko pointed to the role of an unconscious fear of success in some cases of athletic failure (53), and as Mahl (52) pointed out, defenses may also serve to mitigate objectively painful situations. The following case illustrates how psychodynamic conflict may lead to a sudden performance failure.

*Case 3.* An 18-year-old high school senior was playing second base for his baseball team in the state championship game, the last game of his high school career. With his team ahead by one run in the bottom of the ninth inning, with runners at first and second bases and two outs, he fielded an easy ground ball. He elected to throw the ball to his shortstop, covering second, for the out that would have ended the game and given his team the championship. Although it was a throw he had completed countless times in his life, this time he threw the ball over the shortstop's head, into left field, enabling one runner to score. On the next play the opponents scored again and won the game.

As he had prepared for this game, the athlete's conscious focus had been wholly devoted to achieving victory. But because he possessed only average talent, he could not look forward to playing in college, and therefore, as he laced his shoes, practiced batting, and ate his pregame meal for the last time, he was inwardly grieving the loss of the sport he loved. To complete the crucial throw was equivalent to ending his career, something he would not do without conflict.

The following example illustrates how psychodynamic factors may prolong recovery from an injury.

*Case 4.* A college sprinter, in her second year of school at an institution far from home, was discouraged by the failure of her hamstring injury to heal in spite of standard rehabilitation measures. She was thinking of quitting her sport, but if she did she would lose her college scholarship, and she felt that her mother would then be angry with her. She reported that a friend of hers had had "the same thing" happen in the previous year, and the friend had quit and returned home. When asked, the sprinter reported that the friend's mother had been happy to have her daughter home. She then admitted, with some relief, that her own mother missed her and she missed her mother and that a reunion would be a welcome event. This athlete's longing for her mother conflicted with her desire to return to training.

Psychodynamic factors may also contribute to problems between coaches and athletes. The coach may be perceived as a surrogate parent by the athlete (54). In individual sports especially, the athlete-coach relationship may be among the most intimate in the lives of both parties. The intense consideration given to the functioning of the athlete's body may kindle transferences not unlike those in psychotherapy, except that these transferences are usually unexamined. According to Freud, "Psycho-analytic treatment does not create transferences, it merely brings them to light" (55, p.

117). Both sexual acting out and outbreaks of unmanageable hostility sometimes occur.

As always, it is advisable to evaluate each instance of sports-related difficulty before coming to a diagnosis (13). Not all performance syndromes are related to psychodynamic factors, as the following case illustrates.

*Case 5.* A basketball player who too frequently committed senseless fouls and made poor passes at crucial moments appeared to have no motive for doing so. He was happy with his team, his coach, and his general circumstances. It was observed that on one occasion he did precisely the opposite of what his frantic coach instructed from the sideline. Upon further history it was revealed that, until his late teens, this athlete needed to reverse his shoes before putting them on, in order to perceive, concretely, which of two possible arrangements was the best one. He also suffered from symptoms of dyslexia in speech and writing. When the coach said, "Don't foul" or "Don't throw it away," the athlete was confused by the negative construction. The coach was advised to use positive linguistic framing, which quickly alleviated the difficulty.

Nicholi (50) and Collins et al. (34), among others, have mentioned the reluctance of athletes to acknowledge emotional vulnerability. Defensive denial of the psychological sources of trouble may take the form of euphemisms, such as "head case" and "brain lock," or excuses. The following is an example of such a case.

*Case 6.* A distance runner explained her repeated slumps as being due to a series of hard-to-diagnose physical conditions: ferratin-deficiency anemia, diffuse intravascular candidiasis, and "overtraining." With each diagnosis came a torrent of bitter recrimination at the medical community for failing to diagnose her problem earlier.

The athlete in a slump may resort to magic and superstition (56), reflecting a belief, akin to our own, that the source of the trouble lies outside conscious control. Perhaps, as Beisser suggested (11), it is the intangibility of thought, an opponent against which no concrete action can be taken, that leads to athletes' reluctance to acknowledge psychological sources of failure. But this question has not been well studied, and it is not known whether athletes' attitudes toward their own psychological dynamics are any different from those of nonathletes. For the time being, it seems best to treat the athlete's skepticism with the same consideration we have for any resistance (57).

The psychodynamic aspects of sports-related problems may be similar to those that contribute to some defined mental disorders. For example, "choking" may be analogous to panic disorder, and adjustment disorder may present as a slump. Without further study, the construction of a formal nosology in sport psychiatry is premature.

## POSSIBLE OCCUPATIONAL SYNDROME

Lay observers have asserted that society exerts a harmful influence on the personality of the exceptional athlete, fostering tendencies toward violence, promiscuity, and grandiosity. Telander (58) and Bissinger (59) documented in journalistic works the effects of corruption and degradation on young star athletes. As long ago as the fifth century B.C., Euripides opined, "Of all the countless evils throughout Hellas none is worse than the race of athletes. Slaves of their belly and their jaw they know not how to live well. . . . I blame the custom of the Hellenes who, honoring useless pleasures, gather to see such men" (60).

In a thoughtful account of his life in professional basketball, Bill Bradley (49) discussed society's tendency to both worship and condemn its athletic heroes, and he said that as a result the athlete's "sense of identity is insufficient" (49, p. 123). Similarly, I have referred to the "hollow identity" of some professional athletes (14).

Although Ogilvie and Tutko (61), in a nonreviewed publication, expressed the view that whatever personality traits successful athletes display are the result of a "ruthless selection process" (61, p. 61), occupational psychiatry has known since the work of Sherman in 1927 (62) that an individual's adaptation to his or her job is a complex process. There may be a number of factors within the biopsychosocial matrix of an exceptional athlete's life that promote aggressivity, promiscuity, and narcissistic vulnerability.

Nicholi (50) mentioned the struggles of his professional football players with unmanageable aggression, citing violent nightmares as a symptom. He attributed this to a kind of posttraumatic stress disorder, although in his subjects it may also have been a consequence of the use of anabolic steroids, which sometimes promote aggressive behaviors (17). It is also possible, as Bradley seemed to suggest, that in adapting to idolatry the athlete becomes increasingly grandiose and in adapting to degradation he becomes increasingly insecure.

An additional factor may be the fact that the social pressures on professional athletes act within a particular phase of the life cycle. At an age when, according to Erikson (38), a young adult is establishing methods for handling the dilemmas and commitments of intimacy, the professional athlete is also thrust forward into complicated tasks normally characteristic of the later stage of generativity. The predictable apprenticeship that young adults initially enjoy in their professional lives is a luxury denied the professional athlete, whose career depends on immediate output. This condensation of stages may be overwhelming to the person, as Nicholi described (50), and as a result the athlete may remain mired in regressive patterns of behavior that one former athlete called "terminal adolescent syndrome" (63, p. 6).

Another possible factor is athletic training itself. The training that characterizes athletic maturity is strongly narcissistic. The extreme devotion to one's body ensures this. It is possible that athletic training, which is ego-syntonic, shapes other aspects of behavior as a kind of inappropriately applied template, promoting grandiosity and entitlement in human relations and a preoccupation with physical satisfaction. The result of such a process is illustrated by the following example.

*Case 7.* A recently retired professional baseball player returned to his alma mater to carry out certain obligations as a prominent alumnus. A religious man, he was married to an attractive professional woman and worked in the field of human services.

In the evening, he went with some old friends to a nightclub, where his presence was announced from the stage. From his seat he fastened a hard, predatory stare on a woman sitting at a neighboring table with her male companion. After what appeared to be a wordless, visual rape continued for some time, the boyfriend rose from his chair to approach the athlete's table. Instead of the challenge that the whole gathering expected, the boyfriend asked for the athlete's autograph and shook his hand. Afterward the athlete explained his practice of compulsive seductivity as something he learned in professional baseball. The sanctioning of his behavior in the nightclub repeated a pattern that occurred many times over, in various ways, during his career.

In the *Iliad,* Homer provided a vivid description of a narcissistically wounded athlete (64). Achilles, the great runner, was described as a ruthless, arrogant killer. He was the sacker of 12 cities and king of the Myrmidons, known not only for their violent and rapacious inclinations but also for their love of sports. His only vulnerable spot was his heel, by which his mother had held him when she dipped him in the river Styx.

When King Agamemnon took away one of his female prizes, Achilles sulked, refusing to join the battle for Troy, nursing his grudge, and repudiating offers of amends. It was not because of longing for the woman that he pouted—he had women by the score—but rather because of his wounded pride and "bitter humiliation" (64, p. 171). As Achilles pouted, his savage but idle Myrmidons played sports: archery, discus throwing, and chariot racing.

Without further research we are not yet in a position to say whether the problems of professional athletes represent anything more than cluster B personality variants (*DSM-III-R*). But if it turns out that a constellation of aggressivity, promiscuity, and narcissistic grandiosity and vulnerability is in some way an occupational hazard for professional athletes, as lay observers tend to believe, we may somewhat whimsically term this constellation "the Achilles complex" after that ancient athletic king.

## MENTAL ILLNESS IN ATHLETES

Several reports have addressed mental illness among athletes. Beisser (11) reported in detail seven cases of severe illness. Coleman (65) discovered more than 70 cases of suicide among active and retired professional baseball players. In a presentation at the 1987 National Conference of Sport Psychology sponsored by the United States Olympic Committee, James McGee, Ph.D., estimated that 34% of the 250 athletes in one professional sport organization qualified for a substance abuse diagnosis according to *DSM-III-R* criteria.

An attempt to distinguish mental illness among athletic individuals from mental illness among nonathletes was made by Little (66). In a series of 72 men consecutively referred to an outpatient psychiatric clinic, he found that patients who scored high on a scale of athleticism differed from those who did not in several respects. Compared with the nonathletic group, the athletic group displayed more somatic symptoms, better premorbid mental health, and more disorders precipitated by injury or physical illness.

In all of the reports except McGee's the preponderance of subjects were past their athletic prime. There may be several reasons for this. First, it has been suggested (11) that for some people athletic participation may serve as a defense against problems of self-esteem, which become apparent when the athlete retires. The palliative effects of sports may underlie their use as a therapeutic modality in hospitals (67) and their possible effects on mood (21).

Second, athletic behaviors sometimes resemble symptoms of mental disorder and thereby confound recognition of illness. Endurance athletes, for example, pay scrupulous attention to diet and leanness, are relatively hyperactive, and, in the case of some women, experience amenorrhea; for these reasons, they may resemble patients with anorexia nervosa (15). Like Binswager's patient Ellen West (68), endurance athletes often keep detailed diaries. It is possible that coaches of anorexic athletes misinterpret a person's pathological behavior as devotion to training. A preliminary study of body image among marathon runners (69), however, failed to show body image distortions such as those seen in the disease.

A third possibility is that a tendency to idealize athletics leads observers to deny the existence of psychiatric symptoms. One psychiatrist failed to observe any signs of anxiety among a group of professional football players in treatment for drug abuse (34). In his treatise *Sport: A Philosophic Inquiry,* Weiss defined athletes as "excellence in the guise of men" (70, p. 17). To the extent that such a definition is unconsciously shared by clinical observers, it may be expected to interfere with the perception of signs of illness.

Until more case studies of athletes are reported, it will be difficult to draw conclusions about the possibility of distinguishing pathological characteristics among various athletic populations.

## TREATMENT ISSUES

Although published accounts of the treatment of athletes are few, the treatment modalities that have been used are diverse. In 1928 Deutsch (71) reported a psychoanalysis with an athlete, in which she attributed the patient's talent for ball games to unresolved castration anxiety. Psychotherapy (11), group therapy (34, 50), a family systems perspective (72), and pharmacotherapy (73) have been applied. In addition, behavior therapies developed by sport psychology to enhance athletic performance have been used by psychiatrists (13, 50). A nonclinical but interesting phenomenologic approach to training was reported by the philosopher Herrigel (74).

Since the literature is meager, it is not possible to formulate at this time which modalities are appropriate for which problems under various conditions. But our treatment approach may be modified on occasion by the athletic context. For example, an episode of anxiety that might be relatively minor if it occurred in the context of another activity might require urgent attention if it occurred in an athlete facing imminent competition. In providing consultation to teams, it may be necessary to conduct interviews in unusual settings, such as on the sideline or on the team bus (75) and to be respectfully aware of the informal "treatment" that coaches often give players on athletic teams.

The effects of medication on athletes in training is an uncharted area, and caution should be used in prescribing some psychotropic medications because of their effects on vision, coordination, and cardiac function (76). For example, medications that affect visual accommodation may be safe for an interior lineman in football but hazardous to a baseball player.

The psychiatrist should also consider performance variables in prescribing medications. In addition to ECG effects, there have been reports of negative inotropic responses to phenothiazines and tricyclics (77). Thus, these medications may be expected to impair performance in endurance sports in which cardiac output is maximal. One report (78) indicated that cardiovascular performance assessed during treadmill exercise testing is not affected by long-term lithium therapy. Buspirone, which is minimally sedating, may be a useful choice in treating anxiety. Finally, it should be kept in mind that some medications are illegal in some sports. Beta blockers, for example, are forbidden in archery.

Therapeutic eclecticism is sometimes appropriate for the treatment of sports-related problems. The following example illustrates how psychodynamic principles were used in constructing a behaviorist script.

*Case 8.* A recreational downhill skier was troubled by his inability to ski freely down the fall line and his tendency to ski laterally back and forth in great controlled loops. He found this particularly embarrassing on ski trips with corporate colleagues, feeling that it revealed a lack of manliness and courage. He requested instruction in relaxation and rehearsal techniques.

As a youngster he had been discouraged from skiing by his father, who regarded it as an "upscale," "WASP" sport that was inappropriate for his son. Further examination of his history revealed troubling competitive themes, and this psychodynamic information was used in constructing behavioral rehearsal scripts. He was told to imagine himself sharing a lift with a confident, blond Adonis figure who, on the ride, ridiculed skiers taking broad, transverse loops. As his anxiety rose, he was asked to imagine himself giving his companion a karate chop to the Adam's apple, throwing him off the lift, and whisking by his crumpled figure on the way down. His joyful indulgence of this fantasy in the office seemed to loosen his inhibition on the slope.

It might be expected that competitive themes would be prominent in psychiatrists' psychotherapeutic relationships with some athletes. The frequency of such themes is not known, but the following example illustrates a therapist's experience of feeling played with.

*Case 9.* A baseball pitcher sought therapy for, he said, "a problem I am having." He did not say explicitly what this problem was, but over the course of four sessions he threw out various tantalizing suggestions, each of which was followed up by the psychiatrist, without result. After four meetings the patient ended the work. The psychiatrist still had no idea of why the athlete had come to see him and felt as if he had been thrown a series of difficult verbal pitches.

Countertransference issues may also be influenced by the athletic context. A psychiatrist who is a sports fan may derive vicarious gratification from the exploits of the patient. A psychiatrist may prescribe controlled drugs in the interest of enhancing performance (75), may give pregame pep talks (50), and may appear at press conferences to explain a patient's treatment (79). The psychiatrist may overidentify with the athlete in ways the athlete does not appreciate, as suggested by the following example.

*Case 10.* A divorced champion Olympic discus thrower was returning to training after several years of retirement. He consulted a psychiatrist to discuss his feelings about being single again after a number of years of marriage and his anxieties about dating.

One day, in a discussion of his training, the athlete mentioned certain problems he was having with "bending and blocking." The psychiatrist compared these problems with his own difficulty in bending over to field ground balls in his softball games. "Bending" and "blocking" are technical terms in discus throwing, and the patient felt the doctor was seeing a similarity between them that did not exist. He felt misunderstood and in response stopped his therapy.

In adapting treatment to the athletic context, it is important not to forget basic principles. If one important clinical task in general psychiatry is to listen empathetically to the patient's troubles, then we should do so in sport psychiatry. Skilled listening is one feature that distinguishes our work from that of other areas of sport medicine. An interesting account of the importance of listening to athletes can be found in one of the earliest works of Western literature.

In the *Odyssey* (80), Homer described how King Alcineus, observing the tears of Odysseus during a welcoming banquet, suggested that the gathering engage in sports to lift the mood of his athletic guest. Although Odysseus quickly became playful and energetic during the games, his bleak mood soon returned when they were over. Perceiving his "relapse," Alcineus then tried what psychiatrists try first: "Explain to us," he said, "what secret sorrow makes you weep . . . for a sympathetic friend can be quite as dear as a brother" (80, p. 138).

## DISCUSSION

Although an estimated $4 billion is spent annually on sport medicine services (81), the study and treatment of athletes by psychiatry is still in its infancy. A significant contribution of sport psychiatry to sport medicine will depend on an expanded clinical literature. Of particular interest are cases in which children have been traumatized and cases in which adult athletes have suffered sports-related problems. Cases in which athletes are treated for psychiatric disorders are important for integrating sport psychiatry into the mainstream of clinical practice. In addition, consulting work with athletic teams, whose primary mission is to win, needs to be reported on and understood in the context of community psychiatry and group therapy.

The question of how psychodynamic factors influence performance is also of interest. The full expression of aggression seems to be essential for athletic success (82). But we sometimes observe that a particularly good competitor—that is, one who is not merely competitively disposed but, rather, performs best in the most important competitions—feels respectful and friendly toward the opponent. Such feelings were revealed in a private tape-recorded conversation between two heavyweight boxing champions, who were opponents but expressed a warm, admiring relationship (83). If it turns out that such an attitude is characteristic of other champion competitors, this finding could be of interest to our competitive society.

It is also possible that sport psychiatry may someday contribute to the understanding of mind-body relationships. In his book *Mind, Brain, Body,* Reiser pointed to a need for "conceptual templates" (84, p. 17) to link the study of neurotransmission and neuroendocrinology with psychoanalysis. He offered several hypotheses to explain how meanings may be transduced into biological effects, focusing especially on signal anxiety and the psychophysiology of stress (84). Even an advocate for "autonomous disciplines" as rigorous as Edelson can hope for an "eventual rapprochement between neuroscience and psychoanalysis" (85, p. 156).

In 1973 one of the pioneers of sport medicine, Ernst Jokl, discussed the "physical structure of mind" and concluded that "in as far as it encompasses the search for attachment of mind to the body, science tells us nothing" (86, p. 16). Since then, our understanding of the biological basis of mental disease has advanced greatly, but it is perhaps fair to say that the integration of this knowledge with such psychoanalytic concepts as primary and secondary process, unconscious conflict and defense, and psychic structure awaits the appropriate conceptual templates.

Since Jokl's work, sport science has continued to touch on the possible connections between symbolization and biology. Morgan (87), for example, found that hypnotically induced perceptions of effort during exercise altered some aspects of cardiovascular function even when actual effort was invariant. Suinn (88), building on the work of Jacobson (89), observed electromyographic correlates of skiers mentally rehearsing their runs. In neuroendocrine research (90) it has been shown that circulating β-endorphin levels may under some circumstances rise in anticipation of an athletic event.

While these results do not define conceptual templates, they suggest that athletics may constitute an appropriate experimental field for studying the problem. If it were possible, for example, to identify some biological concomitants of such phenomena as "choking" and slump, and if it were also possible to elucidate some symbolic processes involved, then we might be on a useful scientific path. This is because in sports it is often possible to measure the performance effects of "choking" and slump quite precisely and in a well-defined context. But all of this for now is merely a hope that someday sport psychiatry, in its research, will contribute to the convergence of psychologic and neural science.

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# Can Mildly Depressed Outpatients With Atypical Depression Benefit From Antidepressants?

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*Objective: The authors' goal was to explore the efficacy of antidepressant medications in outpatients with mild depression. Method: Four hundred one outpatients were diagnosed as depressed by* DSM-III *criteria. Atypical Depression Diagnostic Scale criteria were also applied to these patients; these criteria require reactivity of mood plus two of four associated features, including hypersomnia, hyperphagia, leaden paralysis, and pathological sensitivity to rejection. All patients were then randomly treated for 6 weeks with up to 300 mg/day of imipramine, up to 90 mg/day of phenelzine, or placebo. Outcome at 6 weeks was determined by clinical global improvement ratings. The outcomes of patients with entry Hamilton Rating Scale for Depression scores in the low (scores of 12 or lower), medium (scores of 13–15), and high (scores above 16) range were compared. Results: The majority (N=332, 83%) of the 401 depressed patients had definite or probable atypical depression. Among the 140 patients who had low pretreatment Hamilton scale scores, 19 (33%) of 57 given placebo, 25 (60%) of 42 given imipramine, and 34 (83%) of 41 given phenelzine responded. Each of the antidepressants was superior to placebo. Similar findings applied to the patients with medium and high Hamilton scale scores, except that the rates of placebo response were lower (29% and 10%, respectively). Conclusions: These data support the use of antidepressant medication for some mildly depressed patients, at least if they have atypical depression. Too few patients were included who did not have atypical depression to draw conclusions about such patients.*

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Antidepressant medications have often been reserved for more severely depressed patients, while psychotherapy is advocated for individuals having "low-grade" depression (1, 2). The pharmaceutical industry has essentially accepted this dictum by requiring a minimum pretreatment score on a standard rating scale in their applications to the Food and Drug Administration. Typically, studies of new antidepressants require a minimum score of 18 or 20 on the Hamilton Rating Scale for Depression (3). Some support for this position may be found in the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program, which compared two psychotherapies with imipramine and placebo and found a treatment effect for imipramine only among depressed patients who had pretreatment Hamilton depression scale scores of 20 or higher (4). This has been interpreted (5) as indicating the usefulness of supportive psychotherapy for more mildly depressed patients, although, strictly speaking, this is an unwarranted assumption because none of the treatments used was demonstrated to be effective for patients with Hamilton depression scale scores lower than 20. We have previously reported failure to demonstrate the efficacy of desipramine in patients with major depression who had low Hamilton depression scale scores (6) as well as in patients with nonmajor depression (7).

We wondered whether the wisdom of requiring high

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Hamilton depression scale scores for entry into antidepressant trials was warranted. Therefore, we have included in our studies of antidepressants any otherwise eligible patient who met *DSM-III* criteria for major depression or dysthymia, regardless of their pretreatment scores on rating scales such as the Hamilton depression scale. This allowed us to investigate whether "mildly" depressed patients can benefit from antidepressant medication. This report consists of a reanalysis of outcome data from patients entering two studies designed to test our hypothesis that phenelzine is more likely to benefit patients with atypical depression than is imipramine. These studies included 401 patients. We arbitrarily grouped these patients into thirds on the basis of their pretreatment Hamilton depression scale scores. Here we will focus on the 140 patients in the third of the group with the lowest scores, 12 or less, using for comparison purposes the 261 patients from the same study who had higher baseline scores.

## METHOD

### *Patient Sample*

Patients included the majority of outpatients with nonmelancholic depression who sought treatment at a depression evaluation service clinic between October 1979 and May 1987. One hundred forty-three of the patients eligible for the two studies described here were entered instead into trials of investigational medications. These trials generally required nonfecund patients for entry. Nine patients entered a study requiring major depression and Hamilton depression scale scores of 18 or greater, 93 entered into two studies (one with N=71 and one with N=22) requiring Hamilton depression scale scores of 10 or greater, and 41 entered a study having no minimum Hamilton depression scale score. Patients were entered preferentially into one of the investigational drug studies if eligible and agreeable, although none of these investigational studies ran for the entire length of time of the two studies reported here. The two studies reported here ran consecutively from October 1979 through May 1987; data from these studies from a variety of perspectives have been reported (8–12). Patients who dropped out or responded during a 10-day placebo washout period are not included in this report.

Patients had to be 18–65 years of age, physically healthy, meet criteria for a *DSM-III* diagnosis of affective disorder, be considered able to follow a tyramine-free diet, and provide informed consent. Patients with a history of psychosis or mania and patients currently abusing drugs or alcohol were excluded. The Atypical Depression Diagnostic Scale was administered to all patients to determine the presence of atypical depression (8). This instrument assesses presence or absence of the required feature of mood reactivity plus the four hypothesized associated features of atypical depression—hypersomnia, hyperphagia, leaden paralysis, and pathological sensitivity to interpersonal rejection. Mood reactivity plus two associated features are required for definite atypical depression, and mood reactivity plus one associated feature are required for probable atypical depression.

### *Procedure*

Baseline evaluations included a clinical interview to determine *DSM-III* diagnoses as well as administration of the 21-item Hamilton Rating Scale for Depression, the Clinical Global Impression (CGI) (13), and a variety of other measures that will not be reported here. Patients were then treated single-blind with placebo for approximately 10 days and reevaluated. Those who had not responded (response is defined in the next paragraph) were then randomly assigned to receive 50 mg of imipramine, 15 mg of phenelzine, or placebo in gradually increasing doses to a maximum dose of 300 mg/day of imipramine, 90 mg/day of phenelzine, or six capsules of placebo. Patients were seen weekly, and CGI ratings were obtained. After 6 weeks, CGI and Hamilton depression scale scores were again obtained and response was determined. Patients were instructed to follow a low-tyramine diet throughout the study.

### *Definition of Response*

The CGI global improvement score was used to determine response or nonresponse after single-blind administration of placebo and 6 weeks of randomized treatment. A score of 1 ("very much improved") or 2 ("much improved") defined responders. Patients with scores of 3 ("minimally improved") or higher ("unchanged or worse") were nonresponders. We used this scale conservatively, so that patients who were less depressed but still symptomatic would be considered minimally improved and classified as nonresponders.

### *Statistics*

Categorical differences among drugs (response versus nonresponse) were tested for differences for patients grouped according to pretreatment Hamilton depression scores by using two-by-three chi-square. Similarly, differences in response rates among patients grouped by Hamilton scores were tested for each drug.

## RESULTS

Of the 401 patients, 140 had pretreatment Hamilton depression scale scores of 12 or less (low scores), 126 had scores of 13–15 (medium scores), and 135 had scores of 16 or greater (high scores). The table shows their rates of response. Patients with low baseline Hamilton depression scale scores responded to both imipramine and phenelzine significantly more often than to placebo. The most striking difference between the patients with low Hamilton depression scale scores and

**TABLE 1. Response to Placebo, Imipramine, and Phenelzine of 401 Patients Grouped by Pretreatment Scores on the Hamilton Rating Scale for Depression**

| | Placebo[a] | | | Imipramine[b] | | | Phenelzine[c] | | | Comparison | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hamilton Scale Score | Patients Given Drug | Responders N | Responders % | Patients Given Drug | Responders N | Responders % | Patients Given Drug | Responders N | Responders % | $\chi^2$ | df | p |
| 12 or lower (low) (N=140) | 57 | 19 | 33 | 42 | 25 | 60 | 41 | 34 | 83 | 24.12 | 2 | 0.000 |
| Imipramine versus placebo | | | | | | | | | | 6.72 | 1 | 0.01 |
| Phenelzine versus placebo | | | | | | | | | | 23.62 | 1 | 0.000 |
| Phenelzine versus imipramine | | | | | | | | | | 5.53 | 1 | 0.02 |
| 13–15 (medium) (N=126) | 42 | 12 | 29 | 43 | 21 | 49 | 41 | 33 | 80 | 22.75 | 2 | 0.000 |
| Imipramine versus placebo | | | | | | | | | | 3.67 | 1 | 0.06 |
| Phenelzine versus placebo | | | | | | | | | | 22.53 | 1 | 0.000 |
| Phenelzine versus imipramine | | | | | | | | | | 9.16 | 1 | 0.002 |
| 16 or higher (high) (N=135) | 40 | 4 | 10 | 50 | 24 | 48 | 45 | 29 | 64 | 26.82 | 2 | 0.000 |
| Imipramine versus placebo | | | | | | | | | | 14.97 | 1 | 0.000 |
| Phenelzine versus placebo | | | | | | | | | | 26.43 | 1 | 0.000 |
| Phenelzine versus imipramine | | | | | | | | | | | | n.s. |

[a] Two-by-three $\chi^2$=7.13, df=2, p=0.03; low versus medium score, n.s.; low versus high score, $\chi^2$=7.07, df=1, p=0.008; medium versus high score, $\chi^2$=4.50, df=1, p=0.03.

[b] All within-drug chi-square comparisons, n.s.

[c] Two-by-three $\chi^2$=4.76, df=2, p=0.09; low versus medium score, n.s.; low versus high score, $\chi^2$=3.74, df=1, p=0.05; medium versus high score, $\chi^2$=2.74, df=1, p=0.10.

those with higher pretreatment Hamilton scores was in their higher rate of response to placebo. Patients with high Hamilton depression scale scores had a very low rate of response to placebo. The trend toward less of a response to phenelzine among patients with high Hamilton depression scale scores appears to be accounted for by their lower rate of nonspecific response, as estimated by placebo response. That is, the response rate appears to consist of a combination of nonspecific response (i.e., they improved for reasons other than the specific effects of the medication) and specific response (i.e., they needed the medication in order to improve). Since the patients with higher Hamilton depression scale scores seemed to have a lower rate of nonspecific response (as estimated by placebo), their apparent drug response might have been less inflated by nonspecific response. An estimation of rate of "true" drug response, then, is the difference between response rates to medication and placebo and yields an estimate of what percent of the patients "needed" the drug to improve, as opposed to getting better despite having taken a medication. This estimated "true" drug response rate was 27%, 19%, and 38% for imipramine, and 50%, 52%, and 54% for phenelzine in the groups with low, medium, and high initial Hamilton depression scale scores, respectively. Since these drug-placebo differences were similar for the three groups and did not show up as a significant drug by severity interaction, we appear to have demonstrated differences in placebo (i.e., nonspecific) response but no difference in "true" drug response among the groups with different Hamilton scale scores.

One might suspect that less severely depressed patients would tolerate side effects less well than more severely depressed patients. If so, then patients with low Hamilton depression scale scores who were not experiencing a remission in their symptoms might drop out of the study, artificially leaving only those patients who had improved. This would result in an apparent drug effect that in reality would be due to unimproved patients dropping out. In fact, no more patients with low pretreatment Hamilton depression scale scores dropped out on drug than on placebo ($\chi^2$=3.52, df=2, n.s.), and there was no difference between patients with low and high Hamilton depression scale scores in rate of dropouts overall or in each drug group ($\chi^2$=0.11, df=2, n.s.). There is thus no suggestion that differential dropout rates artificially produced the results shown.

## DISCUSSION

These data support the utility of antidepressant medication in depressed patients with mild symptoms (at least as measured by the Hamilton depression scale). The most striking difference between patients with low and high Hamilton depression scale scores was the somewhat greater placebo response in the more mildly depressed patients. Once this nonspecific improvement was taken into account, the responses accounted for by specific effects of the medication (drug response minus placebo response) did not differ across groups with different Hamilton depression scale scores.

Since the pharmaceutical companies often require Hamilton depression scale scores in the upper range for entry into their investigational protocols, what are the implications for subsequently giving antidepressants to patients who would not have been eligible for the studies that demonstrated the drug's efficacy? At least for imipramine and phenelzine, it appears that the likelihood of benefit from these agents over and above what may be expected from placebo effects does not differ between the patients with high Hamilton depression scale scores (likely to be eligible for a pharmaceutical company trial) and those who are too "mildly depressed" for entry into these trials. By limiting their trials to the more severely depressed, however, the companies may be unnecessarily limiting their available pool of potential patients and limiting the generalizability of the results of their efficacy studies.

Results of this study run counter to an earlier report of efficacy of desipramine in more severely depressed patients but not in those with mild depression (i.e., those with a Hamilton depression scale score lower than 14) (6). We feel that the discrepancy occurred because of the small number of patients in that study with low Hamilton depression scale scores (N=32). The current study included approximately four times the number of patients, resulting in much narrower confidence limits and less likelihood of asserting no difference when one exists.

The NIMH Treatment of Depression Collaborative Research Program also failed to demonstrate efficacy of imipramine in mildly depressed outpatients with major depression. Although not explicitly stated in the published results, it appears that among 22 patients with Hamilton depression scale scores lower than 20, 55% responded to imipramine, compared with 38% of 21 placebo-treated patients. Although this was not a significant difference between drug and placebo, it is similar to our own results, but with less than half the sample size. Power analysis suggests that if our own imipramine results are accurate the NIMH study only had a 52% chance of finding a significant result with the sample size they used. They may have erroneously asserted the null hypothesis.

Another issue is the seemingly low rate of placebo response in the patients in the current study. Typical rates of placebo response seen in pharmaceutical trials are in the range of 25%–35%. This was the rate of patients who began with low and medium Hamilton depression scores. Patients with scores of 16 or higher, in the range of patients usually included in pharmaceutical trials, had a significantly lower rate of placebo response—10%. We have several possible explanations for this. First, we may be somewhat more conservative in our use of the Hamilton depression scale and the CGI. If so, our Hamilton depression scale scores and response rates may be somewhat lower than other investigators would obtain with the same patients. Second, 83% of the patients reported here had definite or probable atypical depression (8, 9), a hypothesized form of depressive disorder characterized by reversal of the endogenous features that the Hamilton depression scale captures. Hence, the severity of their disorders may not have been adequately reflected by the Hamilton depression scale, and their rate of placebo response might differ from that of patients with other types of depression. Finally, we rate responses on the CGI conservatively, so that a patient must have improved enough that residual symptoms were minimal or absent. We assume that our conservative approach to judging response decreases the likelihood that nonspecific changes in symptoms would be considered positive responses. This conservative approach might yield a lower rate of placebo response in our patients than others would find. The practical result is that the power of a study to demonstrate effectiveness of a drug would be increased. That is, for a study of a given size, the likelihood of finding a difference between drug and placebo is greater if the placebo response rate is lower. Alternatively, fewer patients are needed to have a given likelihood, say 80%, of showing the difference to be significant.

Some skewing of results may have occurred due to the siphoning off of patients into other studies. For example, the patients accepted into these competing studies included a predominance of men and postmenopausal women, while approximately half of the current group included women of childbearing age. We do not believe that the results were skewed because only one small study involving nine patients required Hamilton depression scale scores of 18 or greater. The other studies required Hamilton depression scale scores of 10 or greater (N=93) or had no Hamilton depression scale score requirement (N=41). Thus, sex and age may have been skewed, but we have not found these to affect medication response, and the Hamilton depression scale data seem not to have been skewed.

Although hypotheses of differential placebo response must remain conjectural at present, the current data seem convincing that antidepressants can be effective in mildly depressed outpatients. The majority of patients with atypical depression who have mild depressive symptoms can benefit from antidepressant medication.

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# White Matter Hyperintensity Signals in Psychiatric and Nonpsychiatric Subjects

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*Objective: As part of an ongoing study investigating the relationship between brain morphology/function and neuropsychological performance in psychopathology, the authors conducted brain magnetic resonance imaging (MRI) studies to investigate the prevalence and psychiatric significance of white matter hyperintensity signals. Method: Brain MRI acquisition was done with 0.5 and 1.5 Tesla Philips scanners. Psychiatric subjects (N=229) and normal volunteers (N=154) were recruited by newspaper and local advertising and by physician referral.* DSM-III-R *criteria were used. White matter hyperintensity signals were rated on a 4-point scale of severity. Prevalence rates and risk ratios were calculated. Results: Prevalence rates of hyperintensity signals in all psychiatric subjects (mean age=34 years, SD=9) and normal volunteers (mean age=34, SD=10) were 6.6% and 9.1%, respectively (a nonsignificant difference). When all psychiatric subjects, subjects under age 45, and subjects age 45 and over in a diagnostic category were considered, there were no statistically significant differences between them and normal volunteers in the same age groups in prevalence of schizophrenia, schizoaffective disorder, bipolar disorder, major depression, and obsessive-compulsive disorder. A significant difference existed between the severity of deep white matter hyperintensity signals in subjects with major depression and normal volunteers. Older age was correlated as a risk factor for white matter hyperintensity signals for psychiatric subjects. Conclusions: These results do not support previous findings of greater prevalence of hyperintensity signals in bipolar disorder. Significantly higher prevalence rates of hyperintensity signals were seen in subjects with major depression only when severity of the deep white matter hyperintensity signals was considered. Older age is an indirect risk factor for the presence of white matter hyperintensity signals, probably as a result of vascular changes associated with concurrent medical illnesses.*

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Magnetic resonance imaging (MRI) using spin-echo pulse sequences has permitted the identification of previously undetected phenomena, one of these being increased signal intensity within deep and periventricular white matter. Increased signal intensity on $T_2$-weighted brain MRI may be caused by numerous processes including hydrocephalus, demyelinating diseases, flow enhancement in slowly flowing vessels, a linear signal from penetrating cortical vessels, sulci, edema, or dilated perivascular spaces (1–8). Many hyperintensity signals remain unexplained, thus giving way to the use of such terms as unidentified (ubiquitous) bright objects, leukoencephalopathy, and subcortical encephalomalacia. This paper will refer to these unexplained increased signals as white matter hyperintensity signals.

Studies have begun to examine white matter hyperintensity signals in a variety of psychiatric populations including depression (9–14), obsessive-compulsive disorder (15), bipolar disorder (16–19), schizophrenia (20–23), panic disorder (24), and dementia (1, 25–31; unpublished 1985 study of G.R. Cherryman et al.). Data to date indicate that patients with bipolar disorder are more likely than age-matched control subjects to have white matter hyperintensity signals (16–19), that subjects with late-onset schizophrenia have a greater prevalence rate of white matter hyperintensity signals than control subjects (18, 21, 22), and that a subcortical arteriosclerotic process may account for the greater prevalence of white matter hyperintensity signals in depression (9–14, 32–34).

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The purpose of this paper is to present recent prevalence data on white matter hyperintensity signals in a large group of psychiatric subjects and normal volunteers. Comparisons will be made to earlier studies when appropriate, and a discussion of etiology and implications will be presented.

## METHOD

As part of an ongoing study investigating the relationship between brain morphology/function and neuropsychological performance in psychopathology, we conducted brain MRI studies to investigate the prevalence and the psychiatric significance of white matter hyperintensity signals. Brain MRI acquisition was performed with 0.5 and 1.5 Tesla Philips scanners (Shelton, Conn.). Spin-echo sequences, employing multiecho technique, in the axial plane with long repetition time (2000/50–100 msec/1: repetition time/echo time/acquisition), were used. Slice thickness was 7 mm except for three MRI scans which used 5-mm and 6-mm slice thickness that showed focal 4–6-mm white matter hyperintensity signals. All scans were done at a university hospital. Eighty-three percent of the normal subjects (N=128) and 54% of the psychiatric subjects (N=124) had 0.5 Tesla MRI scanning. Because of overnight stays for the psychiatric subjects, additional use of the 1.5 Tesla MRI scanner was possible during off hours. More normal subjects had 0.5 Tesla MRI scanning because most normal subjects were scheduled as outpatients.

Psychiatric subjects (N=229) and normal volunteers (N=154) were recruited by newspaper and local advertising and by physician referral. Detailed informed consent was obtained from all subjects. Normal subjects were medically and psychiatrically healthy. Comprehensive screening laboratory tests (SMA-22, CBC, urinalysis, thyroid function) were done, including a urine drug screen, ECG, MRI, and physical and neurological examinations. Normal subjects had to have the following to be included in the study: a negative urine drug screen, normal ECG as read by a cardiologist, normal results on physical examination, no history of diabetes or untreated or uncontrolled hypertension, normal results on neurological examination, normal electrolytes, normal CBC, normal urinalysis, and normal thyroid tests. Normal subjects could not have any Research Diagnostic Criteria lifetime diagnosis except for normal brief depressive episodes after situational loss. All subjects were administered the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) and an extensive neuropsychological battery, and most had a lumbar puncture performed during a short inpatient stay on a research unit. Diagnosis was based on *DSM-III-R* criteria using the SADS-L.

Brain MRI scans were initially read once by one of three university neuroradiologists to determine the presence of white matter hyperintensity signals. One neuroradiologist read 46% of the scans; the remainder were equally divided between the other neuroradiologists. Rating scales were not incorporated for the initial MRI reading. The neuroradiologists were aware only of the subject's age and that the subject was in a research study investigating white matter hyperintensity signals; specific information such as type of psychiatric disorder or comparison status was not made available. Dictated MRI findings were kept of each subject with emphasis concerning white matter hyperintensity signals. Neuroradiologists would comment as to known or unknown etiology of white matter hyperintensity signals. Neuroradiologists randomly reviewed MRI scans from psychiatric and normal subjects as well as 0.5 and 1.5 Tesla MRI scans. Interrater reliability and intraindividual drift were not assessed for the first MRI reading.

From August to December 1990, one neuroradiologist (P.A.H.), unaware of diagnosis, reviewed all scans for which the dictated findings indicated the presence of white matter hyperintensity signals from any cause and an age-matched psychiatric and normal comparison group. A 4-point severity rating scale, modified by Coffey et al. (9), was used that allowed for severity and location of periventricular and deep white matter hyperintensity signals to be noted. Subcortical lesion size and location were also described. This second reading of MRI scans was intended to allow a measure of reliability of repeat readings between raters and to rate severity, size, and location of white matter hyperintensity signals. Prevalence rate was based on the second reading of MRI scans.

An etiological approach to determining a white matter hyperintensity signal was incorporated by the neuroradiologist (P.A.H.) in reading the MRI scans the second time. In essence, if a focal white matter hyperintensity signal was felt to represent a deep cortical sulcus, high signal within a cortical vessel, or any other normal structure, the neuroradiologist did not count it as a white matter hyperintensity signal. Any white matter hyperintensity signal that was felt to be due to a known cause was noted to allow comparison to the previous reading. A total of 36 MRI scans with white matter hyperintensity signals and 33 comparison scans were reread to assess interrater reliability.

Risk ratios were calculated as the prevalence rate among persons with white matter hyperintensity signals in a diagnostic group divided by the prevalence rate among normal comparison subjects in the same age group. Point prevalence rate was calculated as the number of subjects with white matter hyperintensity signals divided by the group size. Tests for significance were based on the Z test for the difference between two proportions, two-tailed analysis, and the Z test for the difference of the means in two groups, two-tailed analysis. Interrater reliability for the presence or absence of white matter hyperintensity signals was assessed by using the kappa statistic for measurement of reliability between the first MRI readings by the three neuroradiologists and the second reading of 69 MRI scans by one neuroradiologist. Simple agreement was calculated as total scans in agreement divided by the total group (N=69).

**TABLE 1. Relation of Diagnosis and Age to Prevalence of White Matter Hyperintensity Signals**

| *DSM-III-R* Diagnosis and Age Group | Age (years) Mean | SD | N | Prevalence of White Matter Hyperintensity Signals (%)[a] | Risk Ratio[b] |
|---|---|---|---|---|---|
| Schizophrenia | 33.2 | 9.0 | 114 | | |
| <45 years | 30.9 | 6.1 | 103 | 2.9 | 0.4 |
| ≥45 years | 52.2 | 6.3 | 11 | 9.1 | 0.6 |
| Schizoaffective disorder | 38.2 | 9.1 | 21 | | |
| <45 years | 35.0 | 6.3 | 17 | 0.0 | 0.0 |
| ≥45 years | 52.0 | 5.6 | 4 | 25.0 | 1.8 |
| Bipolar disorder | 37.7 | 7.6 | 22 | | |
| <45 years | 34.5 | 5.2 | 17 | 5.9 | 0.9 |
| ≥45 years | 48.4 | 3.4 | 5 | 0.0 | 0.0 |
| Major depression | 40.3 | 10.5 | 28 | | |
| <45 years | 33.8 | 5.5 | 18 | 5.5 | 0.8 |
| ≥45 years | 52.5 | 5.6 | 10 | 30.0 | 2.1 |
| Obsessive-compulsive disorder | 33.6 | 9.2 | 9 | | |
| <45 years | 32.2 | 8.2 | 8 | 0.0 | 0.0 |
| ≥45 years | 48.0 | | 1 | 0.0 | 0.0 |
| Organic personality disorder | 37.5 | 13.4 | 2 | | |
| <45 years | 28 | | 1 | 0.0 | 0.0 |
| ≥45 years | 47 | | 1 | 100.0 | 7.0 |
| Brief reactive psychosis | 24.5 | 9.2 | 2 | | |
| <45 years | 24.5 | 9.2 | 2 | 50.0 | 7.4 |
| ≥45 years | | | 0 | | |
| Normal volunteers | 34.0 | 9.5 | 154 | | |
| <45 years | 31.1 | 6.2 | 133 | 6.8 | |
| ≥45 years | 52.3 | 5.7 | 21 | 14.3 | |

[a] Number of individuals with white matter hyperintensity divided by total number in diagnosis and age group.

[b] Prevalence within diagnosis and age group divided by prevalence among appropriate normal volunteers.

**TABLE 2. Severity of White Matter Hyperintensity Signals in Major Depression**

| Rating of Severity | Patients With Major Depression | Normal Volunteers |
|---|---|---|
| Periventricular white matter hyperintensity signals | | |
| 0 | 27 | 148 |
| 1 | 0 | 5 |
| 2 | 0 | 0 |
| 3 | 1 | 1 |
| Deep white matter hyperintensity signals[a] | | |
| 0 | 24 | 145 |
| 1 | 3 | 8 |
| 2 | 0 | 1 |
| 3 | 1 | 0 |

[a] The difference between the two groups was significant (Z=2.45, p<0.03, Z test for two proportions, two-tailed).

## RESULTS

Interrater reliability between the original MRI reading and the follow-up reading (69 scans) gave a kappa of 0.68 (84.1% simple agreement). Sex, race, and magnetic field strength (0.5 versus 1.5 Tesla) did not correlate with the presence or absence of white matter hyperintensity signals. Age correlated with the presence or absence of white matter hyperintensity signals for the psychiatric group ($Z=3.4$, $p<0.001$) but only approached significance for the normal group ($Z=1.6$, $p=0.10$). The mean age for the psychiatric group with white matter hyperintensity signals was 42.8 years (SD=10.4), and for the normal group with white matter hyperintensity signals it was 37.8 years (SD=11.2). Prevalence rates of hyperintensity signals in all psychiatric subjects (mean age=34, SD=9) and normal volunteers (mean age=34, SD=10) were 6.6% and 9.1%, respectively (a nonsignificant difference).

Prevalence rates and risk ratios of normal volunteers and subjects in seven psychiatric diagnostic categories are listed in table 1. In each diagnostic category, results are listed for subjects under age 45 and age 45 and older. When all subjects (under age 45 and age 45 and over) in a diagnostic category were considered, there were no statistically significant differences between them and normal comparison subjects in the same age groups for schizophrenia, schizoaffective disorder, bipolar disorder, major depression, and obsessive-compulsive disorder. For organic personality disorder and brief reactive psychosis, meaningful comparisons were difficult because there were only two subjects in each category.

For major depression, when severity of *periventricular* white matter hyperintensity signals was considered (table 2), no significant difference existed between normal volunteers and subjects. A significant difference existed between the severity of *deep* white matter hyperintensity signals in subjects with major depression and normal volunteers.

## DISCUSSION

This study is unique in that it used a large group of subjects and assessed multiple psychiatric populations for the prevalence and risk of white matter hyperintensity signals. Data in table 1 indicate nonsignificant differences in prevalence rates of white matter hyperintensity signals in the comparison and psychiatric subjects when severity of the white matter hyperintensity signals is not considered. Our findings do not show an association between the presence of white matter hyperintensity signals and a diagnosis of any psychiatric disorder. Organic personality disorder and brief reactive psychosis were each diagnosed in only two subjects; thus, significance is difficult to assess.

It is interesting that these results do not support previous findings of significantly greater prevalence of white matter hyperintensity signals in bipolar and major depression samples. In fact, for bipolar disorder, a reverse trend, while not significant, was evident (risk ratio=0.58, $Z=0.307$) when the entire bipolar group was considered. Subjects with major depression and schizophrenia and normal subjects over the age of 45 had a nonsignificantly higher prevalence rate of white matter hyperintensity signals than those subjects under age 45; this finding may reflect, in part, age-related brain vascular changes. For the entire psychiatric group, age correlated significantly with the presence or absence of white matter hyperintensity signals ($Z=3.4$, $p<0.001$), while for the normal group, this correlation approached significance ($Z=1.6$, $p=0.10$). We feel that this finding is consistent with previous studies (5, 35, 36). If age-related brain vascular changes account for a greater prevalence of white matter hyperintensity signals, then reducing potential risk factors for vascular disease would lower the potential risk. Our normal group excluded patients with known neurological or physical illnesses including diabetes and untreated or uncontrolled hypertension. The stringent selection criteria for normal subjects probably account for the nearly significant correlation between white matter hyperintensity signals and age in this group. Psychiatric subjects did not have to meet these stringent exclusion criteria.

Making comparisons among different studies is difficult because of different methodologies and population sampling techniques. Periventricular capping was not included for analysis in this study unless the neuroradiologist on the second reading felt that it was of greater prominence than what is normally seen in all populations (37, 38). This represents determination of the clinical significance of white matter hyperintensity signals instead of a strict description of the presence or absence of white matter hyperintensity signals. Previous studies have reported one or the other (9, 13, 16, 18). However, when severity of deep white matter hyperintensity signals was considered (table 2), a significant difference ($Z=2.45$, $p<0.03$) existed between subjects with major depression and normal individuals. This significant finding has been reported in previous studies (9, 13).

Interrater reliability for the study of white matter hyperintensity signals has been reported in other studies. Coffey et al. (9, 13) reported a simple agreement of 93% between two MRI raters; no kappa was reported. Rabins et al. reported an interrater reliability using the interclass correlation coefficient of 0.85, which represented good reliability (39). Coffey et al. (personal communication, March 1991) and Rabins et al. have used rating scales that incorporate standard photographs depicting the various severity stages of white matter hyperintensity signals for all of their determinations of severity. For our study, simple agreement was 84.1% with a kappa of 0.68. Of 69 MRI scans reviewed, 58 were in agreement as to the presence or absence of deep white or periventricular white matter disease (36 scans with white matter hyperintensity signals and 33 scans without white matter hyperintensity signals). It is felt that this reliability would have been greater if rating scales using pictorial guidelines had been incorporated.

There are methodological concerns from this study. The use of two different MRI scanners can potentially alter data interpretation. Eighty-three percent of normal and 54% of psychiatric subjects received 0.5 Tesla MRI scanning, while the rest received 1.5 Tesla MRI scanning. Outpatients randomly received either 0.5 or 1.5 Tesla, while inpatient subjects more often received 1.5 Tesla MRI. Of 28 subjects (13 normal and 15 psychiatric subjects) who received 0.5 Tesla MRI and 1.5 Tesla MRI scanning in follow-up after 1 year, there were no differences in scan interpretation, which indicates that no new or previously undetected white matter hyperintensity signals were found. Five subjects had white matter hyperintensity signals on both 0.5 Tesla and 1.5 Tesla MRI. The use of three neuroradiologists to perform the initial MRI reading without interrater reliability is of concern. Due to project limitations, this was not feasible. However, all neuroradiologists were board-certified, evaluated subjects randomly on 0.5 Tesla and 1.5 Tesla MRI, and used the same guidelines for evaluation. The second MRI reading was done by one neuroradiologist using a rating scale. The second rater used an etiological approach to white matter hyperintensity signals. If white matter hyperintensity signals that were explained by known or highly suspected cause are considered, 11 additional subjects would be added, to give a modified prevalence rate of white matter hyperintensity signals from any cause of 9.2% for psychiatric subjects and 12.3% for normal comparison subjects (a nonsignificant difference).

The significance of this large study is that white matter hyperintensity signals, when coded as present versus absent, failed to differentiate psychiatric patients and normal comparison subjects. Significantly greater rates were seen in subjects with major depression only when severity of the deep white matter hyperintensity signals was considered.

Possible explanations for this association include the following: 1) white matter hyperintensity signals (perhaps through vascular changes) are markers for conditions that predispose individuals, especially those with late-onset depression, to the expression of depressive disorders, 2) depressive disorders predispose individuals to the development of white matter hyperintensity signals (i.e., induced hypoperfusion), and 3) an underlying disease process predisposes individuals both to the development of depression and white matter hyperintensity signals. We believe that white matter hyperintensity signals represent subtle anatomical changes that occur as a result of vascular insults, producing an expression of psychiatric symptoms that is determined by location of the vascular insult. Many late-onset psychiatric disorders may in fact be a direct result of such injury. Previous studies support this theory (10, 11, 32). Determination of white matter hyperintensity signals may well represent a noninvasive approach in assessing the likelihood of development of psychiatric symptoms or disorders.

There is a need for continued research in psychiatric populations that uses standardized rating scales with pictorial guidelines for hyperintensity signals that will allow comparisons between levels of severity. The decision to include all hyperintensity signals independent of presumed cause (versus only unexplained hyperintensity signals) remains a controversial issue that can easily influence reported prevalence rates. Studies must define the specific methodologies used to define white matter hyperintensity signals. Studies need to continue to incorporate neuropsychological testing, especially complex tasks and attentional tasks; if, in fact, white matter hyperintensity signals represent anatomical changes that produce psychiatric symptoms, then subtle neuropsychological findings should be evident, as some earlier studies suggest (17, 40).

## CONCLUSIONS

In this assessment of large psychiatric and comparison groups, we found no significant differences in the prevalence rate of white matter hyperintensity signals. A significant difference existed between severity of deep white matter hyperintensity signals in subjects with major depression and normal comparison subjects, as has been reported in earlier studies (9, 13).

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## New Policy Regarding Letters to the Editor

Effective immediately, Letters to the Editor critical of an article published in the *Journal* must be received within 6 weeks of the article's publication. Letters received after the deadline will not be considered and will be returned unreviewed.

# Psychotherapy With Mexican-American Patients

Elisa G. Sanchez, M.D., and Paul C. Mohl, M.D.

*Objective: The authors sought to determine whether 20 years of cultural change have altered the clinical lore and earlier findings that Mexican-Americans are more resistant to psychotherapy than other ethnic groups and less likely to be referred for it. Method: All charts of patients seen on a university hospital psychotherapy service since its inception in 1979 were reviewed in three separate studies. The charts of all cases closed as of 1984, the charts of all active patients during 1985, and the charts of all patients screened for therapy in 1986 were included. Ethnic background, age, sex, education, income, treatment modality recommended, duration of therapy, and outcome (interrupted versus completed therapy) were recorded for each patient. Results: There were minor significant differences between the Mexican-American patients and the Anglo-American patients in age and education. No other significant differences were found. Conclusions: Because of cultural change, altered psychiatric perspectives, and/or the effects of socioeconomic status as a confounding variable in previous studies, the accepted clinical lore and earlier findings about psychotherapy with Mexican-Americans may no longer apply.*

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In the main, our knowledge of psychotherapy with Mexican-American patients has been derived from studies of low-income, poorly educated patients who have sought psychiatric treatment in public mental health facilities. The findings of these studies have been applied to all Mexican-American patients without regard for the distinctiveness of subgroups. According to these studies, Mexican-American patients, as compared to "Anglo" patients, are often chosen for supportive, nonintensive psychotherapies. They also have higher rates of dropping out of treatment and have difficulties in treatment that arise from cultural differences between them and their therapists.

The purpose of this investigation was to reexamine some of these earlier findings. There has been limited research on patients with higher incomes and educational levels. We reviewed data on Mexican-American patients with these characteristics and compared them with a similar group of Anglo-American patients.

Since a large majority of Mexican-Americans belong to lower socioeconomic classes, they have mostly been grouped with low-income patients of different ethnic and racial groups in research on treatment. It has long been noted that patients in the lower social classes are more apt to receive short-term supportive psychotherapy or pharmacologic or other somatic therapies (1). They are believed to be more apt to seek only relief of symptoms, to have a poor understanding of the psychotherapeutic process, and to lack a desire for psychotherapy (2).

Yamamoto et al. (3) found that minority-group patients at a large metropolitan county hospital were more often seen in supportive follow-up therapy. The percentages of Caucasian, Mexican-American, and African-American patients who were offered either individual or group psychotherapy were 50%, 40%, and 33%, respectively. Seventy-eight percent of the Caucasians remained in treatment beyond the 9-month period of the study, compared to 14% of the African-Americans, 51% of the Mexican-Americans, and 3% of the Oriental patients. The interpretation was that Caucasian patients were more popular among therapists because they shared with them values and attitudes that facilitated empathy.

Karno (4) found that what he called "old Americans" were more often offered psychotherapy (25 of 65 patients) than were Mexican-Americans (four of 22) and African-Americans (six of 30). Also, the duration of treatment was longer for the old Americans (21 sessions) than for the Mexican-Americans (14.5 sessions) and the African-Americans (14 sessions). When social

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class was taken into consideration, old Americans were accepted in psychotherapy in higher numbers than the patients of the ethnic groups of the same social classes. This was interpreted as proving that differences in treatment between the old Americans and the ethnic groups were related to ethnicity rather than social class.

The life orientation of low-income and minority patients has been described as less concerned about the way they relate to life and as wanting immediate answers to their needs. They give little importance to verbalization and greater emphasis to action and expect resolution of their psychological distress in the immediate future (5). Consequently, it has been recommended that therapy be limited to segments of six or fewer visits at a time. Afterward, therapy may be renegotiated to maintain specific short-range goals. Role preparation has also been advised for patients beginning therapy (6).

Goin et al. (7) studied the expectations about treatment among a group of low-income patients. They found that a surprisingly large proportion (62%) wanted to talk about their feelings rather than have the doctor do something to make them feel better. This apparent wish for a more dynamically oriented psychotherapy did not correspond, however, to the number of sessions they expected to attend. Sixty-one percent of these patients foresaw less than 10 sessions.

In an analysis of the services received by minority patients in 17 community mental health facilities in the Seattle area, Sue (8) compared four ethnic groups to a Caucasian group. More than 50% of the black, Native American, and Asian-American patients dropped out after one contact with the facility, as compared to 42% of the Chicanos and 30% of the Caucasians. The mean number of sessions was 4.68 for the black patients, 3.28 for the Native Americans, 2.35 for the Asian-Americans, 5.30 for the Chicanos, and 7.96 for the Caucasians.

Acosta (9), studying treatment expectations of Mexican-American and Euro-American outpatients in an east Los Angeles clinic, found that Mexican-American patients expected therapy to last an average of 17 visits, compared to 23 for the Euro-Americans. In another study (10), he found that the reasons given for premature termination of treatment by low-income Mexican-American, black American, and Anglo-American patients were not significantly different.

Yamamoto et al. (11) reported that a difference in race between therapist and patient may hinder the psychotherapeutic process. It may even cause the patient to terminate treatment prematurely if she or he perceives the therapist to be prejudiced. These investigators measured the level of ethnocentricity of a group of therapists and found that it was inversely correlated with the frequency with which the therapists saw minority group patients for six or more visits.

It has been mentioned that therapists often lack the knowledge necessary to work effectively with minority populations and their subgroups. This, along with the presence of racism, is believed to raise prejudicial attitudes against minority groups, with the attendant provision of less intensive, unenthusiastic care (5). However, interest in understanding patients of different cultures seems to be growing, as indicated by recent research. Lopez and Hernandez (12) explored the importance that mental health professionals give to culture in their work. Thirty-nine percent of the clinicians studied rated culture as extremely important in their evaluations, and 83% took culture into consideration with most or all of their culturally different patients.

On the other hand, personal characteristics of Mexican-Americans have been held to account for their infrequent participation in intensive therapy. Karno (4) noted that the passivity and polite, inhibited silence of Mexican-Americans are poor equipment for competing for the attention of a therapist. He also described the relationship of Mexican-Americans to institutional settings as one of external compliance masking internal and hostile rejection. Heiman et al. (13) postulated that strong family loyalty and general mistrust of outsiders are major factors in the reluctance of Mexican-Americans to participate openly in psychotherapy. Yamamoto et al. (11) suggested that minority-group patients, being in a disadvantaged position, have acquired an attitude of distrust, disenchantment, and hopelessness that prepares them to leave treatment earlier.

However, in one study the perception of mental illness of a Mexican-American community was found not to be significantly different from that of a group of Anglo-Americans (14). The Mexican-Americans were more likely than the Anglo-Americans to advise a person with emotional problems to see a physician, had more trust in being helped by a psychiatrist, and were more optimistic about the curability of mental illness.

Although it has been reported that Mexican-Americans feel rejected, uncomfortable, and not understood by Anglo-American therapists (15), in a study of preferences for Mexican-American or Anglo-American therapists, both Mexican-American and Anglo-American students expressed more positive attitudes toward the Anglo-American professionals (16). Also, the two groups did not differ in their expectations of therapist behavior. In another study with Chicano community college students, Furlong et al. (17) found that the counselor's ethnic background did not affect the students' perceptions of the counselor's credibility and attractiveness.

The vast majority of studies addressing these issues reflect data collected in the 1960s and 1970s. Much has changed since then in the status of Mexican-Americans in the United States. There has been a large influx of Latin American immigrants, with much publicity and wide recognition of their growing status as a minority. Television commercials regularly portray Hispanic contexts. A presidential candidate spoke Spanish during his acceptance speech. There is a growing awareness of distinctions within the Latin American community, especially cultural ones based on country of origin. In San Antonio, Mexican-Americans have become a majority and now dominate the city council. In 1980, San Antonio became the first major American city to elect a Mexican-American mayor. But this is only the tip of the iceberg: the assistant city manager, the prelate of the archdiocese, several judges, most state legislators, and several leading newscasters and local talk show hosts are Mexican-Americans—all for the first time in the last decade. These very visible, dramatic changes reflect and result in significantly altered perceptions. They reflect growing acceptance by Anglo-Americans and increasing acculturation and political, social, and economic self-assertion by Mexican-Americans. The results are constant exposure of Anglo-Americans to Mexican-Americans and their styles and culture. An even more important result is the growing self-confidence and security among people of Hispanic background. The question is whether any of these changes will influence the attitudes of patients and therapists toward psychotherapy for Mexican-Americans.

As an institution long dedicated to community service in an area with a substantial Hispanic population, the department of psychiatry at the University of Texas Health Science Center at San Antonio conducted three separate studies of this issue on its psychotherapy service during the 1980s. This research was triggered by clinical observations of many successful Mexican-American patients on the service (as well as some unsuccessful patients of all ethnic origins), as the following brief vignettes indicate.

*Case 1.* Mr. A, a 38-year-old Mexican-American man who worked as a mid-level manager and technical analyst, sought help for depression. He comfortably engaged in exploratory psychotherapy with a male Anglo-American therapist. This therapy rapidly linked his depression to marital issues. At this point some cultural issues arose, as the patient's inclination was to "protect" his wife and only discuss his marriage with a senior male member of his extended family. At times there were feelings of shame for "embarrassing the family" by discussing such problems with an outsider. After these were worked through, the therapy moved on to Mr. A's idealization of his mother and feelings of inadequacy with respect to his father. Therapy terminated after 2 1/2 years of weekly sessions; the depression was gone, the marriage was stable and rewarding, and Mr. A was developing greater self-confidence at work.

*Case 2.* Ms. B was a 21-year-old unmarried Hispanic nursing student who had chronic feelings of emptiness, very erratic relations with men, and excessive drinking. She rapidly became dependently attached to her female Anglo-American therapist and was able to work effectively within this transference, dealing with her feelings of rage and deprivation at having had to care for her younger siblings because of her mother's depression and her father's alcoholism.

*Case 3.* Mr. C was a 42-year-old Mexican-American truck driver with a third-grade education who was referred by the police after being arrested for indecent exposure. His marriage was very traditional: he worked at two jobs, his wife did not drive or speak much English, and their relationship was marked by a rigid division of labor with a clear sense of mutual respect and responsibility. With a Latin American female therapist, Mr. C was able to verbalize his sense of abandonment resulting from his wife's heavy involvement with their first grandchild. This recalled his repeated experiences of loss as a child when his family moved piecemeal and sporadically from Mexico to the United States—first his father came for periods of work, then some older siblings immigrated, then he was placed with an aunt for a time while his mother joined her husband, and finally, he and two other children were brought to San Antonio. He successfully grieved for these losses and was able to open new lines of communication with his wife, developing greater flexibility in their relationship, with no further acting out after 2 years of therapy.

The psychotherapy service where our study took place is designed to offer psychotherapy with resident trainees on a sliding fee scale. In order to enter therapy, patients must call, fill out a preregistration form, call again to set up a screening appointment with a faculty member (all of whom are Anglo-Americans), keep the appointment, and have psychotherapy recommended. Approximately 45% of those who call are eventually assigned a therapist (almost all of whom are Anglo-Americans).

## METHOD

In the summer of 1984 a decision was made to undertake an investigation of psychotherapy with Mexican-American patients. First, the charts of all terminated cases were reviewed with a specific focus on outcome (study 1). Then, a review of the charts of all current active patients focused on longevity in psychotherapy (study 2), and finally, a prospective study was begun which followed all new patients for the next 18 months on a variety of parameters and noted when they terminated therapy (study 3). Study subjects included all current and former patients of the psychotherapy service whose charts were available.

Although chart recording had been erratic, almost all charts written since the inception of the psychotherapy service did include a notation about whether therapy was deemed completed or interrupted as well as the ethnic background of the patient. In study 1 these data were collected from all charts of closed cases (N=286) and subjected to chi-square analysis.

In study 2, data on ethnic background and total number of sessions attended were recorded for all active patients (N=124) and subjected to t tests. Active patients included some who had been seen for 3 or 4 years as well as some who had begun therapy the week before.

Studies 1 and 2 were in the form of "snapshots" to give us an idea of whether we were seeing a pattern similar to that reported in the earlier literature. Charts of closed cases are likely to have early dropouts overrepresented, and charts of active patients are likely to have long-term cases overrepresented.

In study 3, 255 consecutive new patients in 1986 who could be readily assigned to Mexican-American or Anglo-American ethnic groups were followed. Data were collected at intake on ethnic group, age, sex, years of education, monthly income, and modality of treatment recommended. The number of therapy sessions each patient attended over the following months was also recorded.

**TABLE 1. Differences Between Mexican-Americans and Anglo-Americans in a Review of Charts of 286 Former Patients (Study 1) and 255 New Patients Followed Prospectively (Study 3)**

| Variable | Mexican-American Patients | Anglo-American Patients | Analysis | |
|---|---|---|---|---|
| | | | $\chi^2$ (df=1)[a] | p |
| Study 1[b] | | | | |
| Outcome | | | | |
| Interrupted psychotherapy | 52 | 180 | 1.10 | n.s. |
| Completed psychotherapy | 8 | 46 | | |
| Study 3[c] | | | | |
| Sex | | | | |
| Male | 19 | 70 | 0.05 | n.s. |
| Female | 39 | 127 | | |
| Therapy recommendation | | | | |
| Offered psychotherapy | 50 | 158 | 0.71 | n.s. |
| Referred elsewhere | 8 | 39 | | |
| Number of therapy sessions | | | | |
| 0 | 13 | 32 | 0.44 | n.s. |
| >0 | 37 | 126 | | |
| <10 | 18 | 42 | 2.26 | n.s. |
| ≥10 | 19 | 84 | | |
| <20 | 18 | 71 | 0.41 | n.s. |
| ≥20 | 19 | 55 | | |

[a] With Yates' correction.

[b] N=60 for Mexican-American patients; N=226 for Anglo-American patients.

[c] N=58 for Mexican-American patients; N=197 for Anglo-American patients.

## RESULTS

The results are summarized in tables 1 and 2. The only significant differences we found were in age (Mexican-American patients were younger) and education (Mexican-American patients averaged 1 year less than Anglo-American patients, although both groups had generally gone beyond high school). Mexican-American patients did not differ from Anglo-American patients in number of sessions, likelihood of interrupting therapy, how they were handled by the screeners in terms of being offered therapy, and whether therapy was more or less likely to be short-term.

## DISCUSSION

The results of this study were essentially negative, failing to replicate earlier findings that have become accepted clinical lore. The Mexican-American patients of this study were chosen for psychotherapy as often as the Anglo-American patients, and neither duration of therapy nor dropout rates differed significantly between groups. Our failure to replicate the findings of earlier studies is important because it suggests that clinical lore and previous findings may not be as generally applicable as they once seemed.

There are a number of possible explanations for our failure to replicate previous findings. Our study was done in a different time, a different setting, and a different cultural context than most of the earlier ones. The setting—a psychotherapy service, rather than a mental health clinic, in a city that is 50% Hispanic—may well have engendered different attitudes on the part of the screeners and the residents. In addition, the 15–20 years that had elapsed since the earlier studies were a time of growing sensitivity to cross-cultural issues in psychiatry. Both of these factors are part of the changed cultural context in which our study was completed. In particular, the Anglo-American context is one of greater awareness of a significant and growing Hispanic minority that must be accepted and dealt with. Similarly, the last 20 years have been a time of increasing Hispanic pride as well as acculturation.

In the study by Sue (8), all of the ethnic groups had lower levels of income and education than the Caucasians. This could explain the differences in duration of treatment and dropout rates between Anglo-American and Mexican-American patients, which in any case were much less significant than those between the Anglo-American group and the other ethnic groups. The studies by Goin et al. (7) and Acosta (9, 10) further demonstrated that the expectations for short-term therapy and for being actively helped by a therapist were more related to low social class and, possibly, low educational level than to ethnicity. It may be that the earlier findings were never entirely accurate representations of the broad mental health needs of Mexican-Americans. Social class may have been a confounding variable.

In addition, the definition of ethnicity is not as straightforward as it might seem. Self-report, identification by Spanish surnames, and/or identification by staff members have been used in different studies. To avoid confusion in research, Lopez (18) recommended a differentiation between race and ethnic background in self-reports and identification of the countries of origin of patients, their parents, and their grandparents. In our population there were representatives of at least four different subgroups: 1) Mexican-Americans who had lived in south Texas for hundreds of years, 2) highly acculturated descendants of mostly middle-class Mexicans who had emigrated in the 1920s and 1930s to escape political and economic turmoil, 3) less acculturated more-recent immigrants and their children who were mostly uneducated and poor, and 4) Anglo-Americans with Hispanic surnames. This last group was counted as Anglo-American in our study.

Yamamoto et al. (11) demonstrated the negative effects of prejudice on treatment outcome. Although more research on the therapeutic relationship between therapists and ethnically different patients is needed, the difficulty in working with these patients cannot be denied. There will always be cultural issues that should be addressed in therapy regardless of the level of acculturation of the patient. If we add to this the differences in social class, education, and language between therapists and patients, therapy can become a complicated endeavor. Although working with more acculturated and more educated patients facilitates empathy and understanding in therapists, because of therapists' different backgrounds, training, and personal characteristics,

**TABLE 2. Differences Between Mexican-Americans and Anglo-Americans in a Review of Charts of 124 Current Patients (Study 2) and 255 New Patients Followed Prospectively (Study 3)**

| Variable | Mexican-American Patients | | Anglo-American Patients | | Analysis | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t | df | p |
| Study 2[a] | | | | | | | |
| Number of therapy sessions | 36.97[b] | 41.4 | 41.55[c] | 47.6 | 0.48 | 122 | n.s. |
| Study 3[d] | | | | | | | |
| Age (years) | 30.7 | 8.5 | 33.3 | 9.9 | 1.98 | 253 | <0.05 |
| Income (dollars per month) | 812[e] | 747 | 852[f] | 853 | 0.35 | 253 | n.s. |
| Education (years) | 13.2 | 1.9 | 14.3 | 2.4 | 3.25 | 253 | <0.001 |
| Number of therapy sessions | 16.7 | 18.7 | 20.0 | 17.1 | 2.01 | 161 | n.s. |

[a] N=28 for Mexican-American patients; N=96 for Anglo-American patients.
[b] Median=21 sessions; range=0–151.
[c] Median=27 sessions; range=0–229.
[d] N=58 for Mexican-American patients; N=197 for Anglo-American patients.
[e] Median=$725; range=$0–3,700.
[f] Median=$925; range=$0–4,000.

it is possible that some of them may still feel uncomfortable with Mexican-American patients. Some residents working at the psychotherapy service during the time of this study never saw a Mexican-American patient, whereas other residents followed the course of several Mexican-Americans at the same time. Further exploration is needed to clarify whether this reflects the method of assigning patients, the availability of patients at certain times of the year, or the residents' personal preferences. What is clear is the importance of giving residents experience with culturally different patients.

Discrimination has been one of the reasons frequently given to explain underutilization of mental health services by Mexican-American patients. The Kline study (15), describing Mexican-Americans' perception of Anglo-American therapists as cold, exploitive, and insincere, is a good example of these studies. Utilization is the most researched area with respect to the mental health of Mexican-Americans, with studies that date back three decades (18), when discrimination may have been a more intense and widespread problem. More-recent studies that encompassed two different subgroups of Mexican-Americans, low-income patients and college students, depicted Mexican-Americans as having an open and trusting attitude toward therapists and psychiatric treatment (10, 14, 16, 17). Moreover, a growing number of studies and statistical reports have found that Mexican-Americans utilize mental health services in proportion to their representation in the community (18, 19).

Whatever the cause of our failure to replicate the findings of earlier studies, it seems clear that the interaction of ethnic subgroups and the mental health field is an evolving one and that as far as psychotherapy utilization and involvement are concerned, earlier cultural distinctions may no longer be relevant.

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# A Randomized Controlled Study of Psychiatric Consultation Guided by Screening in General Medical Inpatients

James L. Levenson, M.D., Robert M. Hamer, Ph.D., and Louis F. Rossiter, Ph.D.

*Objective: The purpose of the study was to test the hypothesis that psychiatric consultation would reduce health care utilization during and after medical hospitalization. Method: A randomized, double-controlled clinical trial of psychiatric consultation was conducted on the general medical inpatient services of a university hospital. After meeting inclusion criteria, 1,541 patients were screened for depression, anxiety, confusion, and pain over a period of 21 months. The 741 patients with high levels of psychopathology or pain were subdivided into baseline control subjects (N=232), contemporaneous control subjects (N=253), and an experimental consultation group (N=256). The major outcome measures were length of hospital stay and hospital costs. Secondary outcome measures were posthospital health status, rehospitalization rates, and use of outpatient medical care. Results: This study did not demonstrate an effect of experimental psychiatric consultation on hospital resource use or posthospital medical care utilization after adjustment was made for disease severity. Hospital resource use decreased in the entire sample over the 21-month duration of the study. Conclusions: The brief, efficient screen for anxiety, depression, confusion, and pain identified a group of patients who also used more hospital resources, but a single experimental psychiatric consultation did not reduce costs. The double-controlled nature of the design proved essential to avoid being misled by background changes in hospital resource use.*

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Edward Billings began a psychiatric consultation-liaison service at the University of Colorado Hospital in 1934 and reported that over the next 5 years the service led to a reduction in hospital length of stay for medical inpatients with comorbid psychopathology from 28 to 15 days (corresponding to an estimated savings of $43 per patient, since the per diem cost was about $4.00) (1). Since then, little attention has been paid to the study of the effects of psychiatric consultation on health care utilization. Most studies have been retrospective (2–4) and therefore must be interpreted cautiously. One well-designed, prospective, randomized controlled trial demonstrated the cost effectiveness of psychiatric consultation for primary care outpatients with somatization disorder (5). There have been two very small, controlled studies of psychiatric consultation for depressed medical inpatients (6, 7), with mixed results.

Here we report the first large, randomized, controlled trial of psychiatric consultation for general medical inpatients, with health care utilization as the primary outcome studied. We demonstrated previously in our hospital setting that medical inpatients with comorbid psychopathology or pain had significantly longer hospital length of stay and greater costs (8). In this study, we hypothesized that psychiatric consultation would reduce length of stay and other resource use during the hospitalization, as well as reduce health care utilization after discharge.

## METHOD

### *Subjects*

Potential subjects were all patients consecutively admitted between July 1, 1987, and April 30, 1989, to general medical teams at a large urban academic medical center. Patients were not considered for the study if

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**TABLE 1. Demographic and Utilization Variables for Medical Inpatients From Baseline Period and Trial of Psychiatric Screening**

| | Baseline Period (N=455) | | | | Psychiatric Screening Trial (N=1,086) | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | N | % | Mean | SD | N | % | Mean | SD |
| Sex | | | | | | | | |
| Male | 229 | 50.4 | | | 544 | 50.1 | | |
| Female | 226 | 49.6 | | | 542 | 49.9 | | |
| Race[a] | | | | | | | | |
| White | 141 | 31.0 | | | 385 | 35.4 | | |
| Black | 311 | 68.4 | | | 677 | 62.3 | | |
| Primary payer[b] | | | | | | | | |
| Medicaid (or patient was indigent) | 205 | 45.1 | | | 496 | 45.7 | | |
| Medicare | 130 | 28.6 | | | 258 | 23.8 | | |
| Blue Cross or private insurance | 99 | 21.8 | | | 285 | 26.2 | | |
| Age (years) | | | 49.2 | 16.2 | | | 47.0 | 16.8 |
| Length of hospital stay (days) | | | 10.1[c] | 11.1 | | | 9.37[d] | 12.4 |
| DRG weight | | | 1.20 | 0.72 | | | 1.30 | 0.99 |
| TOTSCALE score[e] | | | 163.9 | 156.4 | | | 155.2 | 144.5 |
| Number of discharge diagnoses | | | 5.82 | 3.09 | | | 5.62 | 3.03 |
| Number of procedures | | | 2.20 | 2.20 | | | 2.19 | 2.30 |
| Total hospital costs ($) | | | 6,658 | 9,153 | | | 6,680 | 10,263 |
| Total hospital charges ($) | | | 8,998 | 13,405 | | | 9,002 | 15,533 |

[a] Percents do not total 100 because of small number of nonwhite and nonblack subjects (e.g., Hispanic and Oriental subjects).
[b] Percents do not total 100 because of small number of payers unknown at time of discharge.
[c] Median=6 days; range=1–143 days.
[d] Median=6 days; range=1–249 days.
[e] From SysteMetrics Disease Staging system.

they became unavailable because of early discharge, transfer, or death. For patients with multiple admissions during this period, at most two admissions were used, consisting of the first admission during the baseline period (July 1, 1987, to Feb. 5, 1988) and the first admission during the intervention period (Feb. 6, 1988, to April 30, 1989). Of 2,670 patients considered for the study, 1,129 were excluded. Patients were excluded if they did not speak English (N=20), were judged by the nursing staff to be too physically ill to undergo a brief interview (N=491), or were judged by the screeners to be unwilling (N=295) or unable (N=323) to give informed consent. A total of 1,541 subjects met inclusion criteria and entered the study after giving written consent. As previously reported (8), excluded (baseline) subjects were older, had longer hospital stays, greater disease severity, more procedures, and greater hospital costs and charges, which was anticipated since patients were systematically excluded if they were too ill to be interviewed or too demented to give informed consent.

### *Procedure*

*Protocol.* Patients were approached during the first 24–48 hours after admission and asked to participate in a study of the psychological effects of physical illness. After agreeing to participate, subjects were given the Medical Inpatient Screening Test (9), a composite of instruments measuring anxiety, depression, confusion, and pain. Anxiety and depression were measured with the 23 questions from the Hopkins Symptom Checklist (SCL-90-R) (10) that measure these symptoms. Cognitive dysfunction was identified with the Mini-Mental State examination (11). Pain was measured with visual analog scales. Cutoff scores and their rationale as well as other characteristics of the Medical Inpatient Screening Test have been described previously (8, 9).

Demographics, discharge diagnoses, diagnosis-related group (DRG), length of stay, hospital charges and costs, number of diagnoses, and number of procedures came from computerized hospital records and were matched with Medical Inpatient Screening Test data in our database. Costs were estimated by the hospital by means of a standard-ratio-of-cost-to-charges method based on the Medicare cost report. We used two measures of severity of illness, the DRG weight and the TOTSCALE score from the Disease Staging system of SysteMetrics (12, 13). We chose two because all current measures of disease severity have significant limitations (13). DRG weights serve as the current adjustors for Medicare in its prospective payment system. TOTSCALE incorporates DRG weights in addition to other diagnostic and procedure information to calculate a presumably more sensitive measure of overall disease severity. Demographic, disease severity, and hospital resource use data for patients in the baseline and intervention periods are displayed in table 1. Since some patients in the latter period received the experimental intervention, the two groups cannot be directly compared.

*Design.* The study was divided into two phases, a 6-month baseline period (July 1, 1987, to Feb. 5, 1988; N=455) and a 15-month intervention period (Feb. 6, 1988, to April 30, 1989; N=1,086). Patients in both periods were subdivided into those with high Medical Inpatient Screening Test scores (high levels of psychopathology or pain) and those with low test scores (low levels of psychopathology or pain). Only patients with high test scores (N=741) were subjects for this study. Patients who had high scores during the intervention period and who were randomized to receive psychiatric consultation will be referred to as the experimental group (N=256). There were two control groups, patients with high Medical Inpatient Screening Test scores from the baseline period (henceforth referred to as baseline control subjects; N=232) and patients who had high test scores from the intervention period and were randomized not to receive consultation (referred to as contemporaneous control subjects; N=253). This provided a double-comparison research design in which the experimental group could be compared to both earlier (baseline) control subjects and contemporaneous control subjects. Had we used only baseline control subjects, there would have been a risk of noncontemporaneous control bias (14) if any of the variables changed during the period of the study, a likely occurrence in health care delivery.

We chose to randomize subjects at the level of their ward team rather than by individual subjects. During the intervention period, the five general medical teams each rotated monthly between the experimental and control conditions. Thus, in any given month, three teams were in one condition, and two teams were in the other. Alternating the teams between conditions was intended to produce comparable groups, since the teams were not exactly identical in diagnostic mix. We did not randomize individual subjects, since that would have led to the same physicians caring simultaneously for experimental and control patients, creating a risk of Hawthorne and halo effects (14). We minimized such bias by rotating team condition assignment on the same schedule as the attending and resident physicians who all rotated monthly. We found no evidence of unintended changes in physician behavior caused by the study process (15).

*Experimental intervention.* All high-scoring patients on the intervention teams were assigned to receive a psychiatric consultation, which usually occurred within 24 hours. Experimental consultations were provided by six different psychiatrists over the 15 months. All six had previous experience providing consultations at the hospital. They were not part of the research team and were not informed about the hypotheses of the study. Regular (naturalistic) psychiatric consultation remained available to patients' physicians because it would have been unethical to withhold it. Nonexperimental consultations were provided by different psychiatrists as part of the regular consultation-liaison service. If the patient's physician requested a regular consultation *and* the Medical Inpatient Screening Test triggered an experimental consultation, the patient was seen by the consultant who arrived first. Twenty-one patients in the experimental group received naturalistic consultations, as did 20 contemporaneous control patients. Eight patients with low screening test scores in the intervention period also received naturalistic consultations. We analyzed the data both including and excluding patients who received naturalistic consultations from the experimental and contemporaneous control groups. A total of 158 assigned to the intervention completed experimental consultation. Seventy-seven eligible subjects in the experimental group did not receive consultation because of early discharge, transfer, or death. In our analyses, we did not exclude these 77 patients from the experimental group because to do so would have strongly biased comparisons by eliminating patients with shorter stays and would have artificially inflated length of stay in the experimental group, since there is no clear way to identify and eliminate their counterparts in the control group.

The consultations were not highly structured but followed a standard clinical format (16) that included chart review, patient interview, and contact with physicians, nurses, and family as appropriate. A standard consultation note was placed in each patient's chart including *DSM-III* diagnosis. Each consulting psychiatrist kept a log of the length and number of visits with each patient and the number and types of contacts with others performed as part of the consultation. All consultation notes were reviewed after patient discharge and were rated for concordance with a modified version of Popkin's Consultation-Liaison Outcome Evaluation System (17).

*Follow-up.* All patients in the experimental and contemporaneous control groups were targeted for survey 3 months after discharge with computer-assisted telephone interviews by survey research interviewers. Data were collected on physical functioning (activities of daily living), perceived health status, disability and work loss days, posthospital physician and drug use, financial burden, and current depression and anxiety (SCL-90-R questions). We did not attempt to assess cognitive function or pain over the telephone. Posthospital medical care measured by the interview included emergency room, physician, and clinic visits. We were able to contact 41% (N=197) of the patients, 76% (N=150) of whom completed the interview; the remainder refused (5%, N=10) or did not complete (19%, N=37) the interview. We could not reach 59% (N=281) of the patients because they had no current phone (65%, N=184), never answered (25%, N=70), or were deceased (10%, N=27). Control and intervention subjects were equally represented in those interviewed. There were no differences between those reached and those lost to follow-up on any of the demographic, Medical Inpatient Screening Test, disease severity, or hospitalization variables except for age, sex, and Mini-Mental State score at study entry. Those reached were older (mean ages=56.4 versus 47.1 years; Wilcoxon rank sum Z=1.99, $p<0.05$), were more often women (59% [N=83] versus 45% [N=156]; $\chi^2=8.22$, df=1, $p<0.004$), and had slightly higher Mini-Mental State scores (mean scores=24.8 versus 23.3; Wilcoxon rank sum Z=3.08, $p<0.002$).

While data on rehospitalization were available from the household telephone interview, we used the hospital's database instead, since it provided information for 100% of the baseline and intervention period subjects and presumably was of better validity. While the hospital database would not capture hospitalizations at other hospitals, there is no reason to suspect any difference between experimental and control subjects. We measured the number of rehospitalizations, how soon rehospitalization occurred, and the cumulative hospital days, procedures, costs, and charges that followed (but did not include) the index hospitalization until 6 months after the last subject was discharged. Thus, the period of data on rehospitalization varied with when the subject entered the study, from a minimum of 6 months to a maximum of 21 months for intervention period subjects.

### *Data Analysis*

Had the data been normally distributed, or had the data been transformable to a normal distribution, the optimal analysis would have been a two-factor, fixed-effects analysis of variance (ANOVA), using contrasts to test hypotheses. It is well known that neither length of stay nor total costs (our two primary dependent variables) are normally distributed, but transformations of them are likely to be reasonably normal (18, 19). Log transformations have in the past been shown to make such variables more normally distributed (20, 21), but we explored a subset of the family of Box-Cox transformations (which includes the log transformation). Although some of the variables were transformable to approximate normality, several were intractable. Therefore, we felt it safer to test our hypotheses using nonparametric Wilcoxon rank sum tests.

When attempting to partial out the effects of a covariate (e.g., disease severity), we used the transformed variables and added them as covariates to a fixed-effects, normal-theory ANOVA, producing an analysis of covariance (ANCOVA). Since the transformations did not always produce perfectly normally distributed variables, these results should be interpreted with caution. In addition, we checked our results by using rank ANCOVA, as proposed by Quade (22) and Conover and Iman (23, 24). While Quade (22) proposed the use of aligned ranks in rank ANCOVA, Conover and Iman proposed the use of nonaligned ranks, and we chose the latter course.

In comparing the experimental and contemporaneous control groups, we considered the possibility that results might be skewed by patients with very short or very long hospitalizations. Therefore, we also reanalyzed the data after excluding all patients with admissions of 4 days or less (34% of the sample, N=171), all with admissions of more than 30 days (5% of the sample, N=24), and both.

## RESULTS

### *Effect of Intervention on Hospital Resource Use*

There were no significant differences between baseline control subjects and experimental subjects in any demographic, screening score, DRG group, disease severity, or inpatient outcome variables (table 2). Patients assigned to receive psychiatric consultation did not differ significantly from contemporaneous control subjects on any demographic variable, screening scores, or major DRG group. Contrary to the direction of our hypothesis, the experimental group actually had longer length of stay, more procedures, and higher hospital costs and charges than the contemporaneous control subjects. However, the experimental group also had significantly more severe medical illness than the contemporaneous control subjects. This was reflected in both measures of disease severity and the number of recent hospitalizations before the index hospitalization (mean=0.99, SD=1.86, versus mean=0.59, SD=1.09; Wilcoxon rank sum Z=2.12, $p<0.03$). When severity of illness was partialed out, there were no longer any significant differences between the experimental and contemporaneous control groups in any of the inpatient utilization outcome variables. Further analyses using rank-transformed ANCOVA (22–24) also failed to show any significant differences between the experimental and contemporaneous control groups. Excluding naturalistic consultations did not change the results. Excluding patients with very short stays, very long stays, and both (as described earlier) did not reveal any differences between contemporaneous control and experimental subjects after correction for disease severity. Outcomes did not differ significantly as a function of the medical team or consulting psychiatrist.

### *Effect of Intervention on Posthospital Utilization*

For the segment of the sample who could be located and interviewed at follow-up, there were no differences between contemporaneous control and experimental subjects on activities of daily living score, emergency room visits, physician visits, number of medications, or depression and anxiety scores. Data on rehospitalization were available for the entire sample (table 3). Contemporaneous control and experimental patients did not differ significantly on the number of subsequent hospitalizations, the cumulative length of stay, cumulative number of procedures, or cumulative costs and charges.

Experimental subjects were likely to have their next hospitalization sooner, but this difference disappeared after correction for disease severity. Further analysis using rank-transformed ANCOVA (22–24) showed that a slight effect remained even after adjustment for disease severity (F=4.88, df=1, 484, $p<0.03$), but it is difficult to interpret this small remaining difference in light of the lack of effect shown on the non-rank-transformed analyses. Conover and Iman (23) advised that in this situation the distribution of the variable may be particularly troublesome, and indeed, in this case, the variable both was skewed and had outliers.

### *Consultation Characteristics*

On average, the experimental consultation (N=158) took 1.3 hours for the initial visit; 11.4% (N=18) of the subjects received 1.5 further visits totaling 0.7 hours.

**TABLE 2. Demographic and Utilization Variables for Medical Inpatients With High Levels of Psychopathology Who Did or Did Not Receive Psychiatric Consultation**

| | Experimental Group (N=256) | | | | Contemporaneous Control Group (N=253) | | | | | Baseline Control Group (N=232) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | N | % | Mean | SD | N | % | Mean | SD | Analysis | N | % | Mean | SD | Analysis |
| Sex | | | | | | | | | | | | | | |
| Male | 138 | 53.9 | | | 120 | 47.4 | | | $\chi^2=2.17$, df=1, n.s. | 116 | 50.0 | | | $\chi^2=1.03$, df=1, n.s. |
| Female | 118 | 46.1 | | | 133 | 52.6 | | | | 116 | 50.0 | | | |
| Race[a] | | | | | | | | | | | | | | |
| White | 85 | 33.2 | | | 81 | 32.0 | | | $\chi^2=0.10$, df=1, n.s. | 71 | 30.6 | | | $\chi^2=0.83$, df=1, n.s. |
| Black | 168 | 65.6 | | | 165 | 65.2 | | | | 159 | 68.5 | | | |
| Primary payer[b] | | | | | | | | | | | | | | |
| Medicaid (or patient was indigent) | 130 | 50.8 | | | 123 | 48.6 | | | $\chi^2=0.18$, df=2, n.s. | 112 | 48.3 | | | $\chi^2=0.03$, df=2, n.s. |
| Medicare | 70 | 27.3 | | | 61 | 24.1 | | | | 62 | 26.7 | | | |
| Blue Cross or private insurance | 48 | 18.8 | | | 46 | 18.2 | | | | 38 | 16.4 | | | |
| Age (years) | | | 47.8 | 16.9 | | | 47.7 | 17.5 | Z=0.17, n.s.[c] | | | 49.9 | 16.1 | Z=1.25, n.s.[c] |
| Length of hospital stay (days) | | | 11.3[d] | 11.7 | | | 10.2[e] | 18.3 | Z=2.49, p<0.02[c] | | | 11.3[f] | 12.3 | Z=0.10, n.s.[c] |
| DRG weight | | | 1.38 | 1.21 | | | 1.19 | 0.73 | Z=2.28, p<0.02[c] | | | 1.17 | 0.62 | Z=0.97, n.s.[c] |
| TOTSCALE score[g] | | | 170.6 | 179.9 | | | 139.4 | 102.3 | Z=2.03, p<0.04[c] | | | 165.1 | 145.7 | Z=0.97, n.s.[c] |
| Number of discharge diagnoses | | | 6.19 | 3.26 | | | 5.70 | 3.00 | Z=1.64, n.s.[c] | | | 6.22 | 3.19 | Z=0.006, n.s.[c] |
| Number of procedures | | | 2.30 | 2.35 | | | 1.87 | 2.30 | Z=2.12, p<0.04[c] | | | 2.41 | 2.29 | Z=0.82, n.s.[c] |
| Total hospital costs ($) | | | 8,160 | 11,650 | | | 6,358 | 8,833 | Z=2.53, p<0.02[c] | | | 7,509 | 10,389 | Z=0.34, n.s.[c] |
| Total hospital charges ($) | | | 11,109 | 17,587 | | | 8,465 | 12,296 | Z=2.82, p<0.005[c] | | | 10,039 | 15,130 | Z=0.41, n.s.[c] |

[a] Percents do not total 100 because of small number of nonwhite and nonblack subjects (e.g., Hispanic and Oriental subjects).
[b] Percents do not total 100 because of small number of payers unknown at time of discharge.
[c] Wilcoxon rank sum test.
[d] Median=7 days; range=1–70 days.
[e] Median=5 days; range=1–249 days.
[f] Median=7 days; range=1–107 days.
[g] From SysteMetrics Disease Staging system.

**TABLE 3. Rehospitalization Variables for Medical Inpatients With High Levels of Psychopathology Who Did or Did Not Receive Psychiatric Consultation**

| | Experimental Group (N=256) | | | Contemporaneous Control Group (N=253) | | | |
|---|---|---|---|---|---|---|---|
| Variable | N | Mean | SD | N | Mean | SD | Analysis[a] |
| Number of rehospitalizations | 256 | 1.24 | 2.07 | 252 | 1.43 | 2.30 | Z=0.44, n.s. |
| Time to next hospitalization (days) | 256 | 146.9 | 131.4 | 252 | 176.8 | 153.7 | Z=2.09, p<0.04 |
| Cumulative length of stay (days) | 256 | 14.7 | 27.6 | 252 | 16.6 | 29.8 | Z=0.18, n.s. |
| Cumulative procedures | 256 | 1.57 | 2.73 | 252 | 1.98 | 3.46 | Z=0.87, n.s. |
| Cumulative costs ($) | 256 | 9,541 | 23,296 | 252 | 11,759 | 23,729 | Z=0.58, n.s. |
| Cumulative changes ($) | 256 | 13,504 | 35,119 | 252 | 16,452 | 34,562 | Z=0.60, n.s. |

[a] Wilcoxon rank sum test.

There were no significant differences between different psychiatrists in the experimental consultation process, reflected in time spent or contacts made. In experimental consultations, psychiatrists gave a *DSM-III* diagnosis to 82.0% (N=119) of the subjects (the remaining 18.0% [N=26] had no psychiatric diagnosis), made recommendations regarding drug therapy in 29.2% (N=42), and made recommendations for diagnostic procedures in 44.4% (N=64). Chart review demonstrated physician concordance with the psychiatrist in 44.1% (N=52) of the psychiatric diagnoses, 52.4% (N=22) of the drug recommendations, and 32.8% (N=21) of the diagnostic procedure recommendations.

Naturalistic consultations took slightly longer than experimental consultations (J.L. Levenson, unpublished data). While diagnoses and drug and procedure recommendations were made with similar frequency, overall physician concordance was twice as high with naturalistic consultations. The distribution of psychiatric diagnoses differed as well (table 4).

**TABLE 4. Psychiatric Diagnoses of Medical Inpatients With High Levels of Psychopathology Who Received Psychiatric Consultations During Experimental Trial or Under Naturalistic Conditions**

| *DSM-III* Diagnosis | Experimental Consultations (N=145)[a] N | Experimental Consultations (N=145)[a] % | Naturalistic Consultations (N=30)[a] N | Naturalistic Consultations (N=30)[a] % |
|---|---|---|---|---|
| Axis I | | | | |
| Organic and cognitive mental disorders | 67 | 46 | 4 | 13 |
| Substance abuse | 53 | 37 | 6 | 20 |
| Adjustment disorders | 22 | 15 | 8 | 27 |
| Affective disorders | 15 | 10 | 5 | 17 |
| Anxiety disorders | 6 | 4 | 4 | 13 |
| Somatoform disorders and psychological factor affecting physical condition | 4 | 3 | 3 | 10 |
| Schizophrenia | 1 | 1 | 1 | 3 |
| Other | 1 | 1 | 1 | 3 |
| Axis II | | | | |
| Personality disorders | 22 | 15 | 6 | 20 |
| No psychiatric diagnosis | 26 | 18 | 4 | 13 |

[a]Columns add to more than total N and more than 100% because some subjects had multiple diagnoses.

## DISCUSSION

The experimental and control groups did not differ in any of the measured outcomes during and after hospitalization after correction for differences in medical disease severity. There are a number of possible explanations for this, some of which reflect the limitations of this study. While we had demonstrated that the psychopathology and pain for which we screened were associated with greater health care costs (8), the causal relationships are far from clear. Evidence of greater utilization does not address whether comorbid psychopathology is modifiable (or even whether modifying it will reduce utilization). Organic mental disorders and substance abuse accounted for 63% of the psychiatric diagnoses in patients who received the experimental consultations; these conditions are much harder to modify with a brief intervention than most other psychiatric conditions. The prevalence of substance abuse in our sample is especially striking since we had not screened for it directly. The inclusion of pain in our screening is unlikely to be the explanation for so much substance abuse in the sample, since only 11% of the group with high scores on the Medical Inpatient Screening Test had high levels of pain. There may be specific subgroups of patients (defined by medical or psychiatric diagnoses) for whom psychiatric consultation might reduce health care utilization. The best known example is somatization disorder (5), which has a clearer causal effect on utilization than anxiety, depression, cognitive dysfunction, or pain. Either our screen did not identify such potential subgroups or they were "lost" by being submerged in the larger overall subject pool.

The results might have been different had the study been conducted in a different patient population. The majority of our patients were black and poor. Social factors such as poverty may have hampered our ability to have an effect on psychopathology or confounded the effects of psychopathology on utilization. Instability of residence and lack of telephones interfered with our ability to reach patients for follow-up after hospitalization.

Our primary hypothesis was that a psychiatric consultation would reduce length of stay. It seems likely in retrospect that it would be harder to demonstrate utilization reductions in medical inpatients than in outpatients in the current era. Cost containment and other forces have dramatically changed the length and pace of medical hospitalization. In designing this study, we based our power calculations on the ability to detect a change in length of stay of 1 day, or about 9%, because our economist (L.F.R.) viewed that as a reasonable estimate of a substantial change in length of stay. Between the time of those calculations and the beginning of our study, length of stay for general medical patients in our hospital declined about 1 day. Length of stay declined further from our 6-month baseline period to the final 6 months of the intervention period (10.1 versus 8.9 days; Wilcoxon rank sum Z=2.92, $p<0.004$). Such decreases make it more difficult for any intervention to produce further reduction. The brevity of patients' hospitalizations also weakened our intervention, as consulting psychiatrists usually did not have the opportunity to see patients more than once. It should be noted that these changes occurring in length of stay independent of the study intervention validate the importance of our double-control design and its superiority over a comparison of only experimental and noncontemporaneous (baseline) control subjects.

The brevity of the experimental consultations, usually a single visit, leaves open the possibility that more intensive consultation-liaison interventions could have measurable effects on utilization and costs. Another possible explanation of our inability to demonstrate cost benefits of psychiatric consultation is that we studied *experimental,* not naturally occurring, consultations. As noted earlier, we did not randomize naturalistic psychiatric consultation because it is regarded as part of standard care and would be unethical to withhold. There are a number of differences between natural and experimental consultations that might make the latter less effective. Natural consultations occur when physicians request them to help patients with evident psychopathology that often interferes with their medical care. Experimental consultations were triggered by a screen that identified a much larger pool of patients with a different diagnostic mix (table 4). A likely more potent limitation in experimental consultations is that patients' physicians had not *asked* for them. From clinical experience, one would suspect that physicians would pay less attention to unrequested consultations. In fact, we discovered that while experimental and naturalistic consultations were similar in length and content of the initial visit, physician concordance was much lower in experimental consultation, i.e., physicians heeded the psychiatrist's advice much less often. The ethically mandated use of an experimental consultation model that is not fully generalizable to naturalistic consultations remains a continuing difficulty for researchers in this field.

A final reason for our results regarding impact of the intervention is that we included those patients in the experimental group who did not receive the assigned consultation in our analyses comparing experimental and control groups. As explained previously, their exclusion would have artificially inflated the length of stay in the experimental group. Including them diluted any potential effect of the intervention, making it more difficult to prove our hypotheses.

In conclusion, our brief, efficient screening process identified patients with high levels of psychopathology or pain who used more hospital resources, but a simple experimental consultation intervention did not reduce costs. Whether cost benefits can be demonstrated for particular subgroups or with a different intervention requires further study. This report has examined the presence or absence of cost savings, which should not be confused with assessment of the clinical benefits of psychiatric consultation for unrecognized psychopathology. The primary purpose of psychiatric consultation is to aid primary physicians in their diagnosis and management of patients, not to save money. Finally, the value of a double-controlled design was evident because of changes over time in inpatient length of stay and costs that could have otherwise confounded our results.

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# Increasing Frequency of the Diagnosis of Obsessive-Compulsive Disorder

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*Objective: This study attempted to document a hypothesized increase in the frequency of the diagnosis of obsessive-compulsive disorder at a large psychiatric teaching hospital and to investigate correlates of this trend. Method: The annual rates of psychiatric discharge diagnoses at the hospital from 1969 to 1990 were reviewed, and the frequency of the diagnosis of obsessive-compulsive disorder was compared with that of paranoid disorders. Correlations were also done on these diagnostic rates and the rates of reports in the literature in the same years on each of these types of disorders and their treatment. Results: The frequency of the diagnosis of obsessive-compulsive disorder, but not paranoid disorders, increased markedly during the 1980s. This increase was associated strongly and selectively with increases in publications about that disorder, particularly reports on drug and behavior therapy. Conclusions: There has been a large recent increase in the rate of diagnosis of obsessive-compulsive disorder, evidently associated with advances in the study and treatment of the disorder. The observations suggest the influence of a treatment-oriented diagnostic bias in which clinicians may more readily consider and diagnose a condition for which an innovative or effective treatment is available.*

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It has been our impression that the diagnosis of obsessive-compulsive disorder has become more frequent recently. If there has been such a change, there is no reason to assume an increase in the incidence of the disorder. Instead, recent therapeutic advances, particularly the use of inhibitors of serotonin uptake and the use of behavior therapy, may have encouraged consideration of this diagnosis. Earlier, similar "clinician bias" was thought to account for relative increases in the diagnosis of schizophrenia in the 1950s and manic-depressive illness in the 1960s following the introduction of neuroleptics and lithium salts, respectively (1). To test the hypothesis that the diagnosis of obsessive-compulsive disorder has been rising along with more frequent research reports on the disorder, we reviewed the annual rates of discharge diagnoses of obsessive-compulsive disorder at a large university psychiatric hospital and correlated these with worldwide rates of publications on the disorder and its treatment. For comparison, we also collected similar data for paranoid disorders, as few advances in the treatment of these disorders have occurred recently (2).

## METHOD

Discharge diagnostic data were collected from the medical records department at McLean Hospital for the years 1969–1990. The proportion of patients with discharge diagnoses of obsessive-compulsive disorder out of all discharge diagnoses was calculated for each year. For comparison purposes, the proportion of patients with discharge diagnoses of paranoid disorders (which were similarly prevalent in the early 1970s) was also calculated for each year. The group of paranoid disorders included *DSM-II* acute paranoid reaction, involutional paranoid state, and other paranoid state, as well as paranoia; *DSM-III* paranoid disorder; and *DSM-III-R* delusional disorder. If more than one disorder was present, only patients with the index disorder listed first were included in this analysis.

In addition, a computer-assisted literature search using the MEDLINE database (3) was performed to identify research reports on obsessive-compulsive disorder and paranoid disorders and their treatment for the

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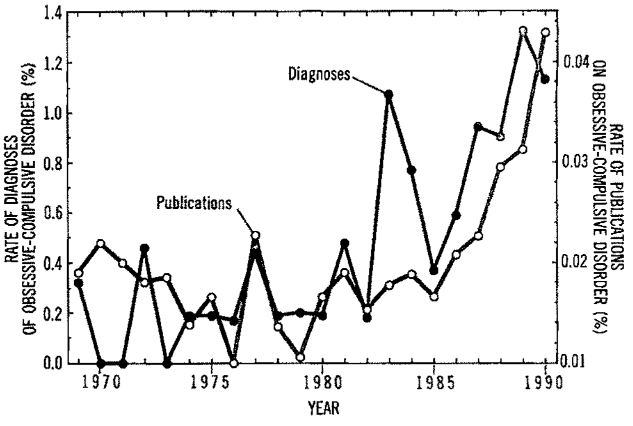
same years. Rates of publication for the disorders were expressed as percentages of the total number of publications in the database per year, to control for an overall increase in research reports of more than 70% during the last two decades. Data are presented as means and standard deviations unless otherwise stated. Rates were compared by t tests, and correlations were computed by nonparametric Spearman rank-order tests.

## RESULTS

From 1969 to 1990, the proportion of patients discharged annually from McLean Hospital with diagnoses of obsessive-compulsive disorder increased more than fourfold (figure 1), from low rates of 0.2%–0.5% in the 1970s (1969–1979 annual mean=0.196%, SD=0.161%) to more than 1.0% by 1983, with high rates sustained throughout the 1980s (1980–1990 annual mean=0.772%, SD=0.388%) (t=10.20, df=20, $p<0.0001$). Simultaneously, the average yearly proportion of MEDLINE publications on obsessive-compulsive disorder for the same periods also increased markedly (figure 1), from a mean of 0.017% (SD=0.004%) of reports per year in the 1970s to 0.023% (SD=0.008%) in the 1980s (t=2.23, df=20, $p<0.05$). Reports on the disorder rose 5.5-fold from 1979 (N=28) to 1990 (N=154). In the 1970s, approximately one-third of the publications on obsessive-compulsive disorder concerned its treatment. In the 1980s, this proportion increased to almost one-half. Correlations between increases in annual diagnosis and publication rates for obsessive-compulsive disorder were highly significant. For all publications on obsessive-compulsive disorder, $r_s=0.54$, N=22, p=0.01, and for reports on all types of treatment, $r_s=0.69$, N=22, p=0.002. Similar correlations were found for reports on pharmacological treatments ($r_s=0.64$, N=22, p=0.003) and behavioral treatments ($r_s=0.67$, N=22, p=0.002).

In contrast to the findings for obsessive-compulsive disorder, the annual frequency of diagnoses of paranoid disorders at McLean Hospital did not change significantly from 1969 to 1990 and even tended to decrease slightly (by 19%). The mean yearly rate of diagnoses of paranoid disorders from 1969 to 1979 was 0.620% (SD=0.407%), compared to 0.500% (SD=0.290%) for the period 1980–1990 (t=0.80, df=20, n.s.). The proportion of MEDLINE publications per year on paranoid disorders also declined in the 1980s, from a mean of 0.015% (SD=0.005%) in 1970–1979 to 0.010% (SD=0.003%) in 1980–1990 (t=2.84, df=20, $p<0.02$). There was no significant correlation between annual diagnostic rates and publication rates for paranoid disorders ($r_s=0.17$, N=22, n.s.).

**FIGURE 1. Annual Rate of Diagnoses of Obsessive-Compulsive Disorder Among All Diagnoses at a Psychiatric Hospital and Annual Rate of Publications on This Disorder Among All Published Medical Research Reports, 1969–1990**



## DISCUSSION

The evident recent increase in the frequency of the diagnosis of obsessive-compulsive disorder in the United States has been associated with significant advances in the study and treatment of the disorder. Obsessive-compulsive disorder is being identified at a much higher rate throughout the United States than was previously suspected (4–7). The increased attention given to this disorder and its treatment may have led to an increased clinical awareness of obsessive-compulsive disorder and greater optimism about its treatability.

During the 1980s, serotonin uptake inhibitors, including clomipramine and fluoxetine, were shown to be effective treatments for obsessive-compulsive disorder (8–10). Fluoxetine (in 1989) and clomipramine (in 1990) have been licensed for general use in the United States and are now widely prescribed (11). In addition, behavior therapy has been shown to be effective in obsessive-compulsive disorder (12, 13), and its use also appears to have become more common.

The strong association that we observed between the rise in the frequency of diagnoses of obsessive-compulsive disorder and the similar increase in journal articles concerning the disorder and its treatment is not likely due to chance alone. It is plausible that the growth of information and the availability of effective treatments for this difficult disorder (4–13) have encouraged clinicians to recognize and diagnose it. Clinicians may be more likely to consider and assign a diagnosis of obsessive-compulsive disorder to a patient when improved treatments and clinical experience with them are available. In our analysis, more than two-thirds of the patients hospitalized with obsessive-compulsive disorder in the late 1980s represented readmissions. This finding suggests that the increased rate of this diagnosis that we observed reflected recent shifts toward giving the diagnosis of obsessive-compulsive disorder to patients previously diagnosed as having other conditions and may represent an example of "diagnostic vogue bias" (14).

This hypothesis of diagnostic bias is consistent with earlier observations of a relative increase in the annual rate of diagnoses of schizophrenia after the introduction of antipsychotic drugs in the 1950s and a shift toward increased diagnosis of manic-depressive illness in the late 1960s after the introduction of lithium treatment in this country (1). Since various habit disorders, such as eating disorders, trichotillomania, kleptomania, and paraphilias, may be related to obsessive-compulsive disorder and also may respond to serotonin uptake inhibitors (15–17), one can expect a similar trend toward their increased recognition and diagnosis.

To evaluate the specificity of changes in the diagnosis of obsessive-compulsive disorder, we performed a similar analysis of annual diagnostic and publication trends for paranoid disorders. This group of disorders was chosen as a comparison syndrome because, unlike obsessive-compulsive disorder, recent advances in the diagnosis and treatment of paranoid disorders have been very limited, and the frequency of these diagnoses at McLean Hospital was similar to that of obsessive-compulsive disorder in the 1970s. Consistent with our hypothesis, there were no significant increases in the rate of diagnosis or the proportion of publications per year for paranoid disorders.

The apparent effect of *DSM-III* on the diagnostic rates of psychiatric disorders at a hospital similar to the site of our study was described recently by Loranger (18). Large shifts occurred in the frequencies of several disorders following the official introduction of *DSM-III* in 1980. For example, *DSM-III* narrowed the definition of schizophrenia and thus almost certainly contributed to decreasing the frequency of this diagnosis. Loranger did not report data for obsessive-compulsive disorder (he only examined disorders with an annual frequency greater than 1%). However, no substantial change occurred in the definition of obsessive-compulsive disorder, since *DSM-III* diagnostic criteria for the disorder were similar to the *DSM-II* criteria used in the 1970s. Moreover, we observed little change in the diagnostic frequency of obsessive-compulsive disorder until 3 years after *DSM-III* was introduced. Thus, it appears that *DSM-III* had little impact on the increased frequency of the disorder found in the late 1980s. However, *DSM-III-R* (published in 1987) substantially altered the diagnostic criteria for obsessive-compulsive disorder, permitting patients to have concurrent psychiatric disorders, such as major depression or Tourette's disorder. Although this alteration, in effect loosening the criteria, may well have contributed to very recent increases in the frequency of diagnoses of obsessive-compulsive disorder, this trend began several years before the introduction of *DSM-III-R*.

In conclusion, there has been a large recent increase in the proportion of inpatients discharged with the diagnosis of obsessive-compulsive disorder at McLean Hospital. This increase may represent a treatment-oriented "diagnostic bias" in which clinicians more readily consider and diagnose a condition for which there are innovative and effective treatments. Further shifts in diagnostic frequencies can be anticipated as more knowledge is acquired about the pathophysiology and treatment of other psychiatric disorders, independent of changes in diagnostic criteria.

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# Oculomotor Performance in Obsessive-Compulsive Disorder

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*Objective: Neuroimaging studies have shown abnormalities of the frontal cortex and basal ganglia in persons with obsessive-compulsive disorder. Since lesions in the frontal cortex and basal ganglia areas affect performance on goal-guided saccadic eye movements, this study investigated the relation between the diagnosis of obsessive-compulsive disorder and oculomotor performance. Method: Eleven patients with the clinical diagnosis of obsessive-compulsive disorder and 14 normal subjects were assessed with respect to their performance on both visual-guided and goal-guided oculomotor tasks. Fixation performance was also measured. Results: The group with obsessive-compulsive disorder had a very significantly greater error rate and a significantly greater rate of inaccurate saccades on the goal-guided antisaccade task, whereas they were not different from the normal group in reaction time, saccadic velocity, and accuracy on the visual-guided saccade task. The distribution of error rates for the patients with obsessive-compulsive disorder was broad, with more than one-half outside the range of the normal group. Most of the abnormal findings were among male patients. Conclusions: The results support the hypothesis of a relationship between impaired performance on goal-guided saccadic eye movement tasks and the diagnosis of obsessive-compulsive disorder, but they also suggest a gender-related subgroup within the group with obsessive-compulsive disorder.*

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The frontal cortex and basal ganglia appear to be involved in obsessive-compulsive disorder (1). Static imaging in research on persons with obsessive-compulsive disorder has demonstrated structural abnormalities in the basal ganglia (2), and positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging studies of brain metabolism and blood flow have observed abnormalities in the orbital-frontal cortical and/or basal ganglia regions (3–6). Pharmacotherapeutic normalization of clinical symptoms of obsessive-compulsive disorder has been associated with normalization of cerebral blood flow and glucose metabolism in both the frontal cortex and the caudate nucleus (7, 8).

Brain circuits involving the frontal cortex and basal ganglia appear to be essential for executing behaviors that are based on internal representations (9). These behaviors may include certain kinds of eye movements, one major class of which is saccadic (from the French *saccade*, meaning "jerk"). Saccadic eye movements can be consciously controlled, directing the line of sight to discrete points in the visual field. Enough is known about the functional neuroanatomy of saccadic oculomotor control to allow investigators to relate saccades with differing degrees of conscious control to certain brain areas. There appear to be two major pathways, anterior and posterior, by which the cerebral cortex can generate saccades.

The anterior pathway projects from the frontal eye fields both directly to the brainstem and indirectly to the brainstem through the superior colliculus (10). This projection is also indirect through the basal ganglia and is involved in generating saccades that are directed by internal models or representations ("goal-guided" saccades) (11). Saccades to remembered targets and saccades to imagined targets are of this type and are under a high degree of conscious control. Performance of goal-guided saccades is vulnerable to lesions involving the frontal eye fields and basal ganglia (12). Lesions in the prefrontal cortex, which projects to the frontal eye fields, also impair goal-guided saccades (12). Frontal lobe lesions and degenerative disorders involving the basal ganglia result in saccadic intrusions and inappropriate reflexive saccades in response to extraneous visual stimuli (13, 14). (In a similar way, apparently "frontal" neuropsychological syndromes can be produced by

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**TABLE 1. Oculomotor Performance of 14 Normal Subjects and 11 Patients With Obsessive-Compulsive Disorder**

| | Normal Subjects | | Patients With Obsessive-Compulsive Disorder | |
|---|---|---|---|---|
| Task | Mean | SD | Mean | SD |
| Fixation | | | | |
| Saccadic intrusions | 2.2 | 3.3 | 4.4 | 3.8 |
| Blinks | 3.7 | 3.6 | 6.7 | 7.9 |
| Temporally random saccades | | | | |
| Reaction time (milliseconds) | 201 | 24 | 206 | 28 |
| Right velocity (degrees per second) | 675 | 251 | 738 | 86 |
| Right accuracy (gain[a]) | 0.93 | 0.05 | 0.93 | 0.05 |
| Left velocity (degrees per second) | 699 | 262 | 682 | 78 |
| Left accuracy (gain[a]) | 0.93 | 0.06 | 0.93 | 0.06 |
| Antisaccades | | | | |
| Errors (proportion)[b] | 0.12 | 0.11 | 0.39 | 0.23 |
| Inaccurate saccades (proportion)[c] | 0.33 | 0.13 | 0.49 | 0.22 |

[a] Ratio of eye movement to target movement.

[b] Significant difference between groups (t=–3.61, df=23, p=0.003).

[c] Significant difference between groups (t=–2.10, df=23, p=0.05).

damage to basal ganglia areas connected to prefrontal areas [15]).

The posterior pathway projects from the posterior parietal cortex and neighboring regions to the superior colliculus and then to the brainstem and is involved in generating "visual-guided" and "reflexive" saccades (12). Such saccades can be considered to be under a lower degree of conscious control than goal-guided saccades. "Spontaneous" saccades do not appear to depend on the cerebral cortex at all and are presumably generated entirely by subcortical structures (16).

On the basis of reports showing frontal lobe and basal ganglia abnormalities in subjects with obsessive-compulsive disorder and the functional neuroanatomy of control of saccadic eye movements, an impairment in goal-guided (but not visual-guided) saccadic performance related to obsessive-compulsive disorder seemed likely. This article reports an experiment to test this hypothesis.

## METHOD

The psychiatric subjects were drawn from a highly selected clinical group. Eleven individuals (five male) with the *DSM-III-R* clinical diagnosis of obsessive-compulsive disorder were recruited from the anxiety disorders clinic at Johns Hopkins Hospital (all diagnoses were made by R.H-S.). Fourteen normal comparison subjects (seven male) were recruited from the hospital staff. All subjects were screened with the Structured Clinical Interview for DSM-III-R (17). Exclusion criteria were any major psychiatric disorder, substance abuse or dependence, and history of injury to the central nervous system. No subjects had schizotypal personality disorder. The mean age of the group with obsessive-compulsive disorder was 39 years (SD=7, range=27–54 years); the mean age of the normal group was 38 years (SD=10, range=22–56 years). All of the subjects with obsessive-compulsive disorder had at least a high school education, and four of the five male subjects had at least a college education. The normal subjects were similarly educated. The family histories of all subjects were negative for obsessive-compulsive disorder and tics, and no subjects reported a family history of schizophrenia.

For the patients with obsessive-compulsive disorder, the mean total score on the Yale-Brown Obsessive Compulsive Scale (18) at the time of diagnostic evaluation was 24.4 (SD=4.5, range=17–30). Their mean score was 12.4 (SD=3.2, range=5–15) on the Yale-Brown obsessions subscale and 12.2 (SD=3.1, range=6–15) on the compulsions subscale. Their mean score on the National Institute of Mental Health Global Obsessive Compulsive Scale (19) was 9.1 (SD=1.1, range=7–11). Only one patient had a history of a tic, but it was not present during oculomotor testing. At the time of oculomotor assessment, one patient was taking clomipramine, one was taking no medication, and the other nine were taking fluoxetine. All 25 subjects had clinically normal magnetic resonance imaging (MRI) brain scans.

Saccadic eye movements were assessed by means of a computerized target presentation/data acquisition system. Targets were presented on an AT-type personal computer with a VGA (640×480 pixels) graphics adapter and monitor. Saccades were recorded with infrared reflection. A chin rest and head restraint minimized head movement. Data acquisition routines sampled horizontal eye movement at 1,000 samples per second.

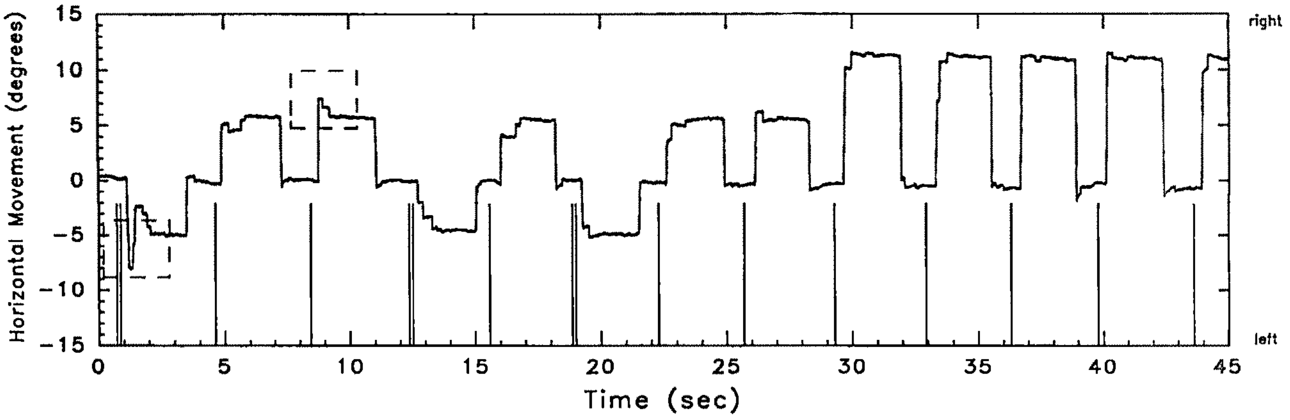
Two tasks were used to assess saccadic performance, and a fixation task was also given. Each task was recorded for 45 seconds. For each, the subjects practiced until they understood the task, in order to reduce the impact of potential generalized learning deficits. The order of tasks was as follows.

*Fixation.* The task consists of fixing the gaze on a small central target and maintaining fixation as well as possible. Square wave jerks (saccadic intrusions) were identified and counted. Square wave jerks are conjugate saccades that move the eyes away from fixation and then, after 100–300 msec, back to the fixation point. The number of blinks was also counted.

*Temporally random saccades.* This task uses spatially regular 20° displacements between left and right targets, with a random time interval ranging from 1 to 3 seconds. Reaction time, saccadic velocity (degree of eye movement per second), and gain (ratio of eye movement to target movement) were measured. The task tests performance on visual-guided saccades.

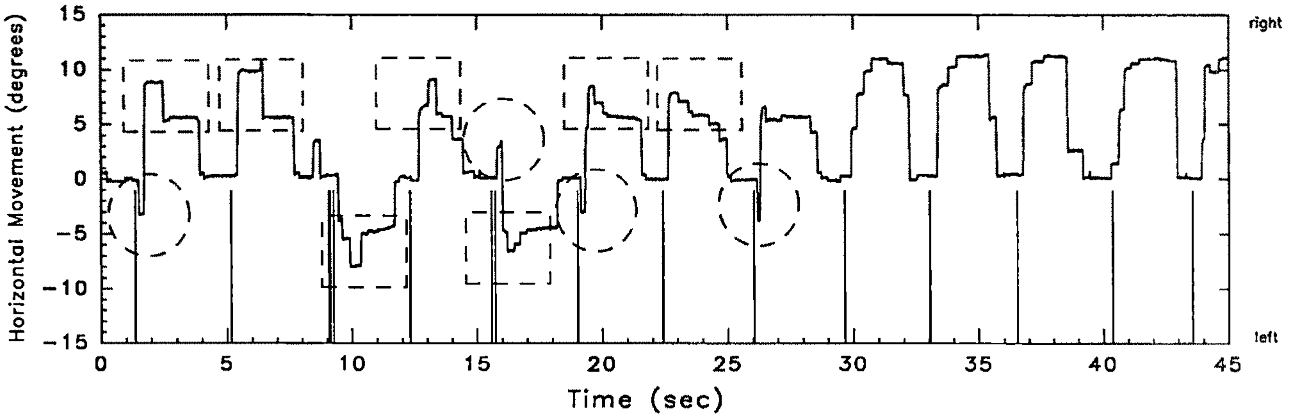
*Antisaccades.* After fixation of a central target, a peripheral target appears simultaneously with the offset of the fixation target. Subjects were instructed to make a saccade to the mirror location opposite that of the target. Subjects were allowed to practice until at least four correct trials were observed. The number of trials

FIGURE 1. Antisaccade Performance of a Normal Subject[a]



[a]Dashed squares enclose inaccurate antisaccades.

FIGURE 2. Antisaccade Performance of a Patient With Obsessive-Compulsive Disorder[a]



[a]Dashed circles enclose saccadic errors; dashed squares enclose inaccurate antisaccades.

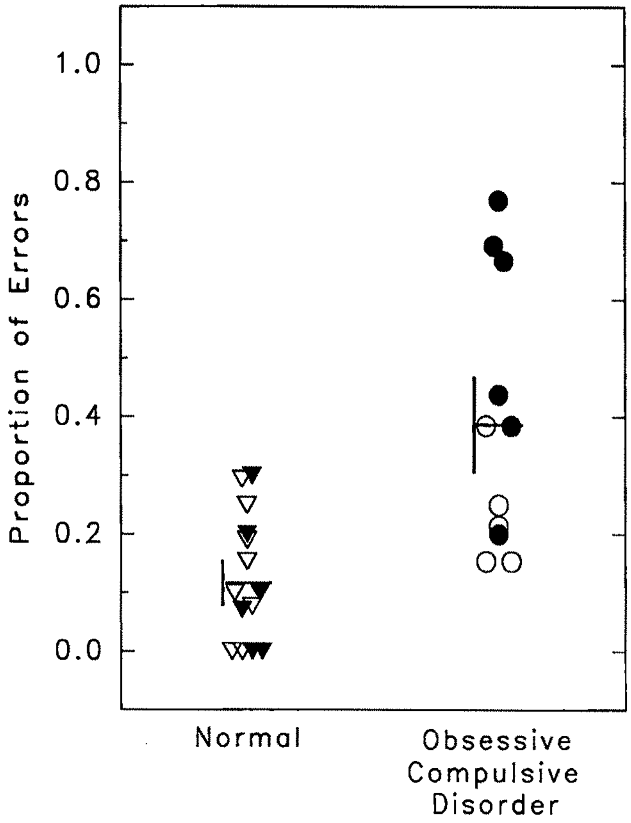
ranged from 10 to 16, as there was a random time delay between trials. Saccades in the wrong direction were counted as errors. Saccades in the correct direction but of inaccurate amplitude—more than 20% different from the correct amplitude—were counted as inaccurate saccades. This task tests the ability to suppress a reflexive saccade in response to a suddenly appearing visual stimulus and to generate a difficult goal-guided saccade.

## RESULTS

On the fixation task there were more blinks and more square wave jerks in the group with obsessive-compulsive disorder than in the normal group (table 1), but these differences were not significantly different at the $p<0.05$ level (independent-sample t tests with separate variance) because of relatively large variance in both groups. Table 1 also shows measures of performance on the temporally random visual-guided saccade task. Mean reaction times were not significantly different between groups, and variance in reaction time also was not significantly different ($F=1.42$, $df=12, 8$, $p=0.56$). Left and right saccadic velocity were not significantly different, but there was more variance in velocity performance in the normal group (for right velocity variance, $F=8.48$, $df=12, 8$, $p=0.009$; for left velocity variance, $F=11.13$, $df=12, 8$, $p=0.004$). Visual-guided saccadic gain or accuracy was identical, within rounding error, for the two groups.

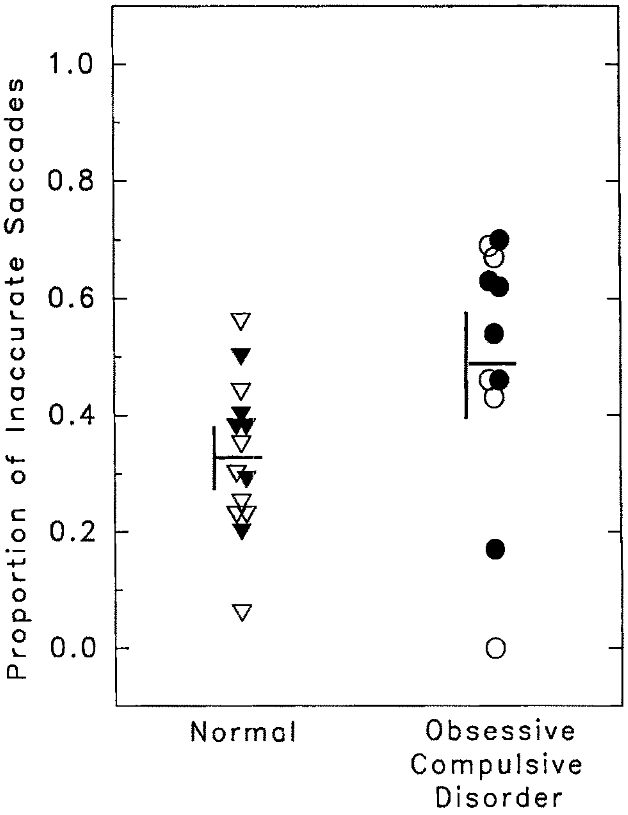
There was a significant difference between the groups in performance on the antisaccade task. Examples of antisaccade performance are shown in figure 1 and figure 2. Figure 1 shows that a normal subject made a very inaccurate saccade on the first trial but subsequently improved in accuracy, with relatively small hypometric or hypermetric inaccuracies. This subject made no errors (saccades toward the antitarget stimuli). Figure 2 shows performance by a patient with obsessive-compulsive disorder. This subject made four errors and also performed poorly in controlling the amplitude of saccades, even when successfully inhibiting reflexive glancing at the antitargets. Performance over the last five tri-

**FIGURE 3. Antisaccade Error Rate of 14 Normal Subjects and 11 Patients With Obsessive-Compulsive Disorder**[a]



[a]Black symbols are male subjects; white symbols are female subjects. Horizontal bars are statistical means; vertical bars are 95% confidence intervals for the means.

**FIGURE 4. Antisaccade Accuracy of 14 Normal Subjects and 11 Patients With Obsessive-Compulsive Disorder**[a]



[a]Black symbols are male subjects; white symbols are female subjects. Horizontal bars are statistical means; vertical bars are 95% confidence intervals for the means.

als improved, but all subjects had demonstrated understanding and ability to do the task during practice before assessment.

On the antisaccade task, the mean proportion of errors was more than three times higher in the group with obsessive-compulsive disorder than in the comparison group (table 1). To analyze gender effects in more detail, the proportion of errors was examined as a dependent variable in a multivariable regression model using diagnosis, gender, and the interaction between diagnosis and gender. The beta for diagnosis was 1.7 (t=3.95, df=1, p=0.001), the beta for gender was 0.05 (t=0.27, df=1, p=0.79), and the beta for the interaction was –1.2 (t=–2.71, df=1, p=0.01) (model F=11.05, df=3, 21, p=0.0001). Thus, although there was a large effect for male subjects with obsessive-compulsive disorder (figure 3), there was still a gender-independent difference in performance between the group with obsessive-compulsive disorder and the normal group.

The proportion of inaccurate saccades in the antisaccade task was analyzed in the same way. The beta for diagnosis was 0.4 (t=0.73, df=1, p=0.48), the beta for gender was –0.1 (t=–0.56, df=1, p=0.58), and the beta for the interaction was –0.1 (t=–0.08, df=1, p=0.94) (model F=1.80, df=3, 21, p=0.18). Diagnosis modeled alone had a beta of 0.4 (t=2.23, df=1, p=0.04) (model F=15.23, df=1, 21, p=0.0007). Thus, there did not appear to be a gender-related difference in antisaccade accuracy, but there was a difference between diagnostic groups (figure 4).

## DISCUSSION

The results support the hypothesis of a deficit in *goal-guided* saccadic performance related to the diagnosis of obsessive-compulsive disorder. The fact that the visual-guided but not the goal-guided saccadic performance of the patients with obsessive-compulsive disorder appeared to be normal supports an inference of frontal cortical and/or basal ganglia functional abnormality underlying this performance deficit. This does not necessarily imply a structural deficit in these areas. It is possible that anxiety alone could account for poorer performance. Although the subjects were rated with the Hamilton Scale for Anxiety at the time of diagnostic interview (and there was no correlation of these ratings with oculomotor performance), a quantitative rating of anxiety at the time of oculomotor testing was not obtained, so this question cannot be answered here.

The gender difference in antisaccade error rate among the subjects with obsessive-compulsive disorder was an unexpected finding. There were no other apparent factors (including age at onset, duration of the disorder, other concurrent diagnoses, family history, and medication) that might have accounted for this difference. Another gender difference has been reported for obsessive-compulsive disorder: a trend for earlier age at onset among males (20). How these findings might be related is unclear, but the two together suggest further study of possible gender differences in obsessive-compulsive disorder.

As in research on eye movements in schizophrenia, although there were significant differences between group means, there was overlap between individuals in each group. Several factors may account for the variability in the group with obsessive-compulsive disorder. The categorical decision on the clinical diagnosis may have been in error. Although it seems unlikely that there were false negative diagnoses in the normal group, there may have been false positive diagnoses in the group with obsessive-compulsive disorder. There may be etiologic heterogeneity for developing obsessive-compulsive disorder, so that only some patients have functional brain pathology. There may be a normal distribution of oculomotor performance, so that even if relative impairment of oculomotor control is invariably associated with obsessive-compulsive disorder, absolute differences from normal are not always observed because a given individual's hypothetical baseline performance was better. In addition, clinical state at the time of testing, medication levels in blood or brain, and perhaps the nature of specific obsessions and compulsions might have effects.

Variability in the normal group could also have been due to a number of factors. For example, there is evidence that poor smooth pursuit eye movement is a manifestation of a latent trait related to schizophrenia (21). Although no subjects reported a family history of schizophrenia, this is probably not a reliable method for determining family history. Furthermore, schizophrenia spectrum conditions such as schizotypal personality disorder were not systematically assessed in the subjects' relatives. These conditions have been associated with poor smooth pursuit eye movement (22) and could possibly be associated with poor antisaccade performance.

Sampling bias might have confounded our findings. Berkson (23) suggested that when any single medical condition is apt to result in treatment with less than perfect certainty, individuals with more than one condition (including unmeasured conditions) are more likely to be in treatment than those with only one. The logic of Berkson's bias implies that individuals in treatment-based samples are more likely to reveal overlap of conditions than those in the general population who have the same conditions. Being in psychiatric treatment may be related to more general deficits in goal-guided or "executive" functioning and thus deficits in goal-guided saccadic eye movements.

## CONCLUSIONS

This is the first report of a deficit in oculomotor control among subjects with the diagnosis of obsessive-compulsive disorder. The results are consistent with evidence from other research suggesting frontal lobe and basal ganglia abnormalities in obsessive-compulsive disorder. However, replication in an independent group is needed. Although no cross-sectional associations were apparent, longitudinal study of relationships between clinical status, medication, and oculomotor performance is indicated. Study of unaffected relatives of patients with obsessive-compulsive disorder would also be of interest. If these results are replicated in a clinical sample, study of community samples will be useful to avoid the possible effects of Berkson's bias (23).

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# Randomized, Double-Blind, Crossover, Placebo-Controlled Comparison of Propranolol and Betaxolol in the Treatment of Neuroleptic-Induced Akathisia

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*Objective: Beta-blocking agents, particularly propranolol, are considered effective in the treatment of neuroleptic-induced akathisia, but considerable controversy exists about the involved receptor subtype(s). The authors conducted a randomized, controlled trial comparing the effects of propranolol and betaxolol to determine whether central $\beta_1$-adrenoceptor blockade is sufficient to correct neuroleptic-induced akathisia. Method: The subjects were 19 patients whose neuroleptic-induced akathisia responded to 20 mg/day of propranolol and subsequently reemerged during a placebo washout period. They were randomly assigned to propranolol (20 or 40 mg/day) or betaxolol (10 or 20 mg/day) and, after another placebo period, were switched to the second β blocker. Results: There was no significant difference in the antiakathisia effects of propranolol and betaxolol. Conclusions: The lack of difference between propranolol and betaxolol suggests that $\beta_1$-adrenoceptor blockade is sufficient to improve neuroleptic-induced akathisia. The results of this explanatory study need therapeutic confirmation.*

(Am J Psychiatry 1992; 149:647–650)

Studies have demonstrated that β blockers, particularly propranolol (1–3), are effective in the treatment of neuroleptic-induced akathisia. A central site of action appears likely because several studies—unfortunately, most of them uncontrolled—have shown that hydrophilic β blockers, such as nadolol (4), atenolol (5, 6), and sotalol (7), are less effective than propranolol, which is highly lipophilic. The site of action of these drugs, however, and the involved receptor subtypes are still controversial.

Zubenko et al. (4) and Derom et al. (5) found that the $\beta_1$-receptor blockers metoprolol and atenolol are less effective than propranolol. Therefore, Zubenko et al. proposed a $\beta_2$-adrenergic mechanism of action in neuroleptic-induced akathisia. This hypothesis was supported by a study by Adler et al. (8), which showed similar efficacy of propranolol and ICI 118,551, a selective $\beta_2$ blocker. On the other hand, a study by Kim et al. (9), which used metoprolol at a dose with preserved $\beta_1$ selectivity, and our previous study using betaxolol (7) failed to demonstrate any difference in efficacy between propranolol and $\beta_1$ blockers. In an attempt to elucidate the receptor subtype(s) involved in the β blockers' effects in neuroleptic-induced akathisia, we performed a double-blind, crossover, placebo-controlled study comparing low doses of two highly lipophilic β blockers: propranolol, which is nonselective ($\beta_1$ and $\beta_2$ blocker), and betaxolol, which is highly $\beta_1$ selective.

## METHOD

We used the akathisia rating scale of Chouinard et al. (10). This includes a subjective evaluation scale rated 0 to 3 and an objective evaluation scale rated 0 to 6; only the latter was used in this study, both for selection of patients and for evaluation of drug effects. The drugs (propranolol, betaxolol, and placebo) were administrated at 8:00 p.m., and all the patients were assessed on the following day between 8:00 and 9:00 a.m., i.e., after a 12-hour interval.

Over 14 months, 68 patients with neuroleptic-induced akathisia underwent observation. The akathisia

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The drugs and the placebo were provided by Synthelabo-France.

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**TABLE 1. Characteristics and Outcome of 19 Subjects Given Crossover Treatment With Propranolol and Betaxolol for Neuroleptic-Induced Akathisia**

| Patient (and sex) | Age (years) | *DSM-III-R* Diagnosis | Drugs | Akathisia Score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Base-line | Propranolol (20 mg/day) | Placebo | Propranolol (mg/day) | | Placebo | Betaxolol (mg/day) | |
| | | | | | | | 20 | 40 | | 10 | 20 |
| 1 (F) | 42 | Chronic paranoid schizophrenia | Haloperidol decanoate, levomepromazine | 4 | 0 | 4 | 0 | | 4 | 0 | |
| 2 (M) | 40 | Chronic paranoid schizophrenia | Flupentixol | 4 | 0 | 4 | 0 | | 4 | 0 | |
| 3 (M) | 38 | Chronic paranoid schizophrenia | Haloperidol decanoate, cyamemazine, trihexyphenidyl | 4 | 0 | 4 | 0 | | 4 | 4 | 4 |
| 4[a] (F) | 50 | Chronic paranoid schizophrenia | Haloperidol decanoate, cyamemazine, tropatrepine | 4 | 0 | 2 | | | | | |
| 5 (M) | 55 | Chronic disorganized schizophrenia | Loxapine, cyamemazine | 4 | 0 | 4 | 4 | 0 | 4 | 4 | 0 |
| 6 (M) | 49 | Moderate mental retardation, intermittent explosive disorder | Flupentixol, trihexyphenidyl | 5 | 0 | 5 | 3 | 0 | 5 | 0 | |
| 7 (M) | 51 | Atypical psychosis | Flupentixol | 6 | 0 | 6 | 0 | | 6 | 0 | |
| 8 (M) | 26 | Chronic undifferentiated schizophrenia | Levomepromazine, pipotiazine, trihexyphenidyl | 4 | 0 | 4 | 0 | | 4 | 0 | |
| 9 (M) | 37 | Chronic paranoid schizophrenia | Haloperidol decanoate, levomepromazine | 4 | 0 | 4 | 0 | | 4 | 0 | |
| 10 (M) | 51 | Chronic paranoid schizophrenia | Droperidol sultopride | 4 | 0 | 4 | 0 | | 5 | 0 | |
| 11[b] (F) | 30 | Borderline personality disorder | Flupentixol, alprazolam | 4 | 0 | 4 | 0 | | 0 | | |
| 12 (M) | 54 | Intermittent explosive disorder, alcohol dependence | Flupentixol, sulpiride | 4 | 0 | 4 | 0 | | 4 | 0 | |
| 13 (M) | 29 | Chronic paranoid schizophrenia | Cyamemazine, haloperidol | 4 | 0 | 4 | 0 | | 5 | 0 | |
| 14[c] (M) | 21 | Chronic paranoid schizophrenia | Pipotiazine | 6 | 0 | 6 | | | | | |
| 15 (M) | 49 | Chronic paranoid schizophrenia | Haloperidol, clomipramine | 4 | 0 | 4 | 0 | | 5 | 0 | |
| 16 (M) | 65 | Bipolar disorder, manic | Haloperidol, chlorpromazine | 6 | 0 | 5 | 0 | | 6 | 0 | |
| 17 (F) | 25 | Chronic undifferentiated schizophrenia | Flupentixol | 5 | 0 | 5 | 0 | | 4 | 0 | |
| 18 (M) | 22 | Chronic paranoid schizophrenia | Flupentixol | 4 | 0 | 4 | 0 | | 5 | 0 | |
| 19 (F) | 25 | Chronic disorganized schizophrenia | Propericiazine | 5 | 0 | 5 | 0 | | 5 | 3 | 0 |

[a] Not included in crossover study.

[b] Dropped out of study.

[c] Excluded from study because of worsening psychiatric status.

of 45 of these patients was rated as 4 or above, so these 45 were preselected for the study. None of them had any condition that was a contraindication to treatment with β blockers. All of them received 20 mg/day of propranolol.

For propranolol treatment to be considered successful, an objective akathisia score of 0 had to be maintained for at least 1 week. After a 1-week washout period with placebo, the akathisia score had to return at least to 4 and to not differ from the initial score by more than 1. These conditions were met by 19 patients.

Of these 19 patients, 18 entered the study and were randomly assigned to propranolol, 20 mg/day, or to betaxolol, 10 mg/day, for up to 10 days. In case of failure, the dose was doubled (40 and 20 mg/day, respectively). The doses of propranolol (20 and 40 mg/day) and betaxolol (10 and 20 mg/day) are considered equipotent (11).

The β blocker was then withdrawn, and the patients received placebo for 3 to 10 days, i.e., until further treatment became necessary. Then the patients received the second drug; in case of failure, the dose was doubled.

Among the 19 patients preselected for the study, 13 had akathisia scores of 4, three had scores of 5, and three had scores of 6. As required by the eligibility criteria, all of the 19 patients achieved a score of 0 with 20 mg/day of propranolol. During the washout period the score of one patient (patient 4) failed to return to its initial level, and she was then excluded from the study. During the first treatment period nine patients received propranolol and nine patients received betaxolol.

During the second placebo sequence the akathisia scores returned to their initial levels for all patients except patient 11, whose score remained zero; therefore, she was withdrawn from the study. The 17 remaining patients received the second β blocker: propranolol for nine and betaxolol for eight. Because of worsening psychiatric status, patient 14 was dropped from the study after 48 hours so his neuroleptic treatment could be changed (haloperidol, 60 mg/day, in place of pipotiazine, 40 mg/day).

We tested order, carryover, and treatment effects with the Wilcoxon rank-sum test, taking into account the design of the trial (two-period crossover clinical trial).

**TABLE 2. Group Akathisia Scores Before and After Crossover Treatment With Propranolol and Betaxolol**

| | | Akathisia Score | |
|---|---|---|---|
| Time and Condition | N | Mean | SD |
| Before study | 19 | | |
| Without drugs | — | 4.44 | 0.73 |
| Propranolol (20 mg/day) | — | 0.00 | 0.00 |
| Placebo | — | 4.38 | 0.62 |
| During study | — | | |
| Patients who received propranolol first | — | | |
| Propranolol[a] | 9 | 0.00 | 0.00 |
| Placebo | 9 | 4.75 | 0.89 |
| Betaxolol[b] | 8 | 0.50 | 1.41 |
| Patients who received betaxolol first | — | | |
| Betaxolol[b] | 9 | 0.00 | 0.00 |
| Placebo | 9 | 4.25 | 0.71 |
| Propranolol[a] | 9 | 0.00 | 0.00 |

[a] 20 or 40 mg/day.
[b] 10 or 20 mg/day.

## RESULTS

It should be kept in mind that this study addressed a highly selected group of patients: 45 subjects with a score of at least 4 on the Chouinard objective akathisia rating scale were preselected, and low doses of propranolol (20 mg/day) completely ameliorated the neuroleptic-induced akathisia of 19 patients (42%).

The individual akathisia scores and background characteristics of the 19 patients are shown in table 1, and group scores appear in table 2. We found no significant difference between the antiakathisia effects of these two highly lipophilic β blockers (treatment effect: $z=0.88$, $p=0.38$; order effect: $z=0.88$, $p=0.38$; carryover effect: $z=-0.88$, $p=0.38$). Furthermore, although an increase in akathisia score of 1 was observed in some patients (patients 10, 13, 15, 16) when active drug was withdrawn, no major rebound effect was observed among our patients.

No difference in the delay before onset of action was observed: the maximal effect was observed within 3 days (propranolol: mean=2.80 days, SD=1.65; betaxolol: mean=2.34 days, SD=1.34), and in no case was there any loss of efficacy.

We had planned to subject all patients to a final placebo period, but this was considered unethical by the hospital investigational review board.

## DISCUSSION

The lack of difference between propranolol, which is a $\beta_1/\beta_2$ blocker, and betaxolol, which is a highly $\beta_1$-selective drug, suggests that $\beta_1$-adrenoceptor blockade is sufficient to improve neuroleptic-induced akathisia. This is in accordance with the results of the study by Kim et al. (9), which used low doses of metoprolol, and with our own previous study of betaxolol (7), but it contradicts the findings of Adler et al. (8), which suggested similar efficacy in $\beta_2$ blockers. Adler et al. proposed a possible "redundancy of the central beta-adrenergic receptor in the CNS."

Because of these confusing results, the possibility that these compounds could have another common property should be considered. Intrinsic sympathomimetic activity can be excluded, since propranolol and betaxolol are devoid of such activity. The membrane-stabilizing property is also unlikely, for two reasons: 1) propranolol possesses this characteristic, but it is considered of clinical relevance only at high doses, which were not attained in our study and are not usual in clinical practice, and 2) betaxolol does not have this property (12, 13).

Finally, $\beta_3$ receptors (14) appear to possess only metabolic action, chiefly in fat tissue, and conventional β blockers exert little or no effect on these receptors.

Nevertheless, from a therapeutic point of view, it is obvious that $\beta_2$ blockade is undesirable because of contraindications and its possible adverse effects (e.g., bronchospasm, vasospasm).

The results of this controlled trial confirm our previous findings and suggest that central $\beta_1$-adrenergic blockade is sufficient to correct objective neuroleptic-induced akathisia.

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# Ethics Complaints Against Female Psychiatrists

Kathleen Mero Mogul, M.D.

*Objective: The purpose of this study was to assess the prevalence and nature of investigated ethics complaints against female psychiatrists and to compare them with those against male psychiatrists. Method: The author, a member of the APA Ethics Committee, reviewed informal records kept by her during a period of just under 5 years. Results: The Ethics Committee reviewed 259 complaints against men and 30 against women, constituting a prevalence rate of about 1.1% against male members and 0.4% against female members. Thirty-nine percent of the complaints against men and 60% against women were dismissed. Eighty-five sexual complaints against male psychiatrists and eight against female psychiatrists (of which two and six, respectively, were for homosexual behavior) were investigated. Also investigated were 19 complaints involving discourtesy or poor judgment against men and two against women, 21 of breach of confidentiality against men and three against women, and 23 involving financial matters against men and four against women. Conclusions: In this study of informal records, there were fewer investigated ethics complaints against female than against male psychiatrists, and more of these were dismissed after investigation. A greater proportion of the complaints of sexual exploitation made against women were for homosexual involvement. Cultural power differentials between genders may in part explain some of the data.*

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Soon after my appointment to the APA Ethics Committee in May 1985, I was struck by the infrequency of complaints against female psychiatrists. For just under 5 years I tracked all cases that came to the Ethics Committee for review, examined the data for information about cases against women, and compared ethics investigations against women with those against men.

Particular attention was paid to cases involving "undue familiarity," that is, physical and sexual involvement of psychiatrists with patients, because they constitute the largest single category of complaints and because they have received so much recent attention in the professions, the professional literature, and the media and from legislatures and licensing bodies.

Moore reviewed the activities of the APA Ethics Committee in 1978 (1) and again in 1985 (2). He reviewed the number of complaints, the kinds of charges made, and the resolutions of the complaints but gave no information about complaints against female psychiatrists. Several books about sexual relations between therapists and their patients similarly fail to address involvement by female psychiatrists (3–5).

Gartrell et al. (6), in their report on a survey of psychiatrists regarding sexual involvement with patients, did break down the data by gender. Twenty percent (N=291) of their respondents were women. Of the responding women 3.1% acknowledged sexual involvement with patients, compared to 7.1% of the male respondents. Of all sexual contacts reported, 3.5% were between female psychiatrists and male patients and 1.4% were between female psychiatrists and female patients, while 7.6% occurred between male psychiatrists and male patients. The remaining 87.5% of cases of sexual involvement were between male psychiatrists and female patients.

## ETHICS COMMITTEE DATA

The data reported here were accumulated in just under 5 years from careful records that I kept. The data are not an official record and are nearly, but perhaps not absolutely, accurate.

For several reasons the number of cases considered in this report are not a measure of the number of complaints lodged during this period. First, district branches report to the APA Ethics Committee only those complaints which undergo a formal investigation. If allegations are judged to be trivial or not to involve

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breaches of *The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry* (7), the complaints are dismissed at the local level without report to the APA Ethics Committee. Thus, there is no information available for comparing the rate or nature of those complaints against male and female psychiatrists which are dismissed after initial scrutiny. Second, as Moore (1, 2) observed, it is unclear how consistently district branches reported to the APA about investigated cases that did not result in effects on membership status. Reporting accuracy has greatly increased, especially under the standardized procedures adopted in 1989 (7). Last, at any time, a significant number of cases are under investigation at the district branch level, to be reported to the national Ethics Committee upon resolution at a future time. Thus, the figures reflect only those cases reviewed by the Ethics Committee (all cases reviewed by each member of the committee) upon their resolution at the district branch level.

The total number of cases reviewed in this period (June 1985–April 1990) was 289 or 0.002 per member per year, that is, in the same range as reported by Moore (1) for prior years. Of the 289 complaints, 259 were against male psychiatrists and 30 were against female psychiatrists. Thus, 10.4% of complaints deemed to merit investigation were against women. APA had about 35,000 members during these years, of whom about 23% were women; that is, there were 27,000 male members and 8,000 female members. (Because of the growth in membership and proportion of women, these figures may somewhat overestimate both membership and percentage of women for the years covered by the data.) The calculated prevalence of reported complaints was 0.4% against female members and 1.1% against male members for the period examined. There were investigated complaints against female psychiatrists less than half as often as there were against men, bearing out the initial impression that complaints against women are comparatively less frequent, although not nearly so infrequent as the impression from raw case figures, unrelated to membership numbers, first conveyed.

The proportion of cases dismissed after investigation, in which insufficient or no evidence of an ethics infraction was found, was greater for women than for men (60% versus 39%).

### *Complaints of Sexual Involvement*

Complaints of sexual involvement constituted the largest single category of complaints against both men and women. Eight women and 85 men were accused of having sexual or intimate physical relationships with patients; these complaints represent 27% of those against women and 33% of those against men and reveal no substantial difference in the proportion of sexual complaints by gender of psychiatrists. A considerable number of additional complaints against men (N=35–40), but not against women, seemed to arise from nonrecognition and/or mismanagement of erotic transference in which no actual sexual contact took place.

Outcomes of accusation of sexual misconduct were also similar for male and female psychiatrists. One (12.5%) of the eight cases against women and 12 (14%) of the 85 against men were dismissed because of lack of credibility of the complainant or insufficient evidence to convince the investigating body. Similarly, five of the eight accused women and 53 of the 85 accused men, constituting about 60% of each group, were either expelled or suspended from membership.

The single clearest difference between the complaints against male and female psychiatrists was in the area of homosexual involvement; only two of 85 complaints against men were for homosexual involvement, but six of eight against women were for involvement with female patients. In contrast to almost all other complaints, neither of the two complaints involving female psychiatrists engaged in sexual relations with male patients came from the patients themselves. In fact, both men defended the psychiatrists against the charge of an unethical act.

### *Other Complaints*

Breach of confidentiality was the complaint in 21 of the cases against men and in three against women. There were 23 complaints against men and four against women involving financial matters (insurance or tax fraud or billing disputes). In these two categories there appeared to be no difference in the proportion of complaints by therapist gender.

Complaints that could be called discourtesy or poor judgment in dealing with patients were made against 19 male psychiatrists but only two female psychiatrists. Eighteen (7%) of the cases against male psychiatrists and four (13%) against female psychiatrists involved complaints about forensic matters. All four forensic cases against women involved work related to child custody or child abuse, and all were dismissed upon investigation because of a finding of no unethical conduct. Eight of the 18 forensic cases against men were related to children. There was one admonishment and one suspension; the other cases were dismissed.

The remaining complaints were in a number of categories, seemed not to show a gender-related pattern, and were not tabulated. They included complaints related to managed care and other administrative practices, professional misrepresentation and false advertising, and those which could be encompassed under "incompetent practice" involving misdiagnosis, treatment mismanagement, lack of coverage, and abandonment. Some complaints remained unclear and appeared to entail suspicious, angry, or even delusional grievances.

## CONCLUSIONS AND DISCUSSION

There are many inherent problems with the data presented, and the implications must be examined with caution and modesty. Certainly no extension of conclusions to the prevalence of unethical practice by psychiatrists, nor even to the number of complaints against them, is warranted. As stated previously, there is no information about the number and nature of complaints dismissed locally without further investigation. Further, it is clear from clinical experience and various other sources, especially with regard to sexual exploitation, that a relatively small number of patients who feel cause for complaint ever lodge a complaint. Even the information regarding investigated complaints reveals that the total number of these complaints against women is low, and numbers in subcategories are so low, that comparisons have little convincing meaning.

With these caveats, it does appear from this study of informal records that there was a lower prevalence of complaints deemed to merit investigation against women than there was against men, that a greater proportion of the complaints against women were found to be groundless on investigation, and that, among sexual complaints against female psychiatrists, a greater proportion related to homosexual involvement.

Far less clearly, the figures indicate some similarities and a few differences in complaints against men and women and in the results of the investigations. The proportions of cases involving complaints of sexual involvement, breach of confidentiality, and of a financial nature appeared similar for both genders. Mismanaged erotic transference (short of physical involvement) and discourtesy-related complaints seemed more common among men, while there seemed to be relatively more complaints about forensic work against women. The similarity in percentages of sexual complaints in this study does not contradict the reports that sexual involvement with patients is less common for female than for male psychiatrists (6), since the prevalence of any complaints against women was only about half that against men.

The data lend some plausibility to power differentials as contributory to the high prevalence of male psychiatrist-female patient sexual involvement, since this is the dyad in which cultural power differences are the greatest. Perhaps female psychiatrists are less likely to initiate an exploitative relationship, especially with male patients in which the power differential is reversed. However, Gartrell et al.'s figures (6) on self-admitted sexual involvement with patients show a greater comparative percentage of sexual involvement with male patients by psychiatrists of both genders. Certainly, other explanations, instead or additionally, are possible for the lower prevalence of sexual exploitation by female psychiatrists. These could include the younger mean age of female psychiatrists, the fact that a larger proportion work in institutional settings, and the fact that, by and large, they treat an even larger proportion of female patients than do their male colleagues.

It also appears, especially taking Gartrell et al.'s data into account, that men are less likely than women to make complaints of having been victimized. In this study no men complained about sexual involvement with their female psychiatrists. In the two such cases, other parties brought the complaints against the doctors, and in the two homosexual complaints against male psychiatrists the complaints were lodged by men about exploitation during their adolescence. In our culture, it may be even more difficult for men than it is for women to acknowledge feeling exploited or victimized.

None of the previous statements is meant to imply that sexual activity with male patients by psychiatrists of either gender is less exploitative of the patient or of the treatment relationship than when female patients are involved, nor that it is less damaging to patients or less unethical.

The preceding speculations are merely an attempt to raise some ways to think about the reported data, and the meagerness of the data makes them even more conjectural. Continued collection of data, broken down by gender, appears justified.

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# Effectiveness and Replicability of Modules for Teaching Social and Instrumental Skills to the Severely Mentally Ill

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*Objective: This study evaluated the effectiveness and replicability of psychoeducational modules designed to improve the social and instrumental competencies of severely mentally ill patients. Method: Staff in seven facilities used the modules to teach 108 severely mentally ill patients. Staff received 2 days of formal training followed by periodic consultation. Each module's effectiveness was measured by a test of the patients' knowledge and performance of the skills taught in that module. Staff's adherence to the instructional techniques specified in the modules was measured by directly observing them and assessing the fidelity of their behaviors to those specified in the modules. Results: The patients' skills significantly improved and were maintained during a 1-year follow-up, and staff accurately followed the modules with minimal consultation. Conclusions: These training modules are effective and replicable techniques for teaching social and instrumental skills to severely mentally ill patients. The modules can be easily disseminated to a variety of facilities and used as components in a comprehensive rehabilitation program.*

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Although neuroleptic medication is the treatment of choice for reducing the positive symptoms of chronic schizophrenia, it does little to ameliorate the anhedonia and impoverished social and instrumental role functioning associated with the disorder's negative symptoms (1, 2). Several comprehensive model psychosocial treatment programs that complement pharmacotherapy by improving social and instrumental role functioning have resulted in reduced rates of relapse and rehospitalization (3–5). Unlike medication, however, they have not been widely adopted by the general systems of mental health care. The programs have been difficult to disseminate because of their comprehensiveness; their use of unique settings, staff, patients, and resources; and their poorly operationalized techniques (6, 7).

Less comprehensive psychosocial treatment programs focusing on improving patients' interpersonal skills have been developed. These programs have also reduced rates of relapse and rehospitalization (8–11), but they too have had little impact on the general systems of mental health care. Their treatment techniques have been poorly documented, and their narrow focus on social or family skills has not satisfied the desire for improved role performance and quality of life for patients, their significant others, and clinicians.

However, a set of psychoeducational modules have been developed with the objectives of 1) teaching patients social and instrumental competencies in key domains of community functioning and 2) being easily and accurately used by staff in general systems of mental health care. The domains include self-management of neuroleptic medication, coping with schizophrenic symptoms, grooming/personal hygiene, participating in recreational activities, and engaging in friendly conversations. These domains were chosen because competency in them has been associated with longer community tenure (12–14) and is hypothesized to be associated with less risk for symptomatic relapse according to the "stress-vulnerability" theory of schizophrenia (15).

All modules use the same highly structured and thoroughly specified instructional techniques so that staff can easily and accurately use them with a minimum of training and ongoing consultation. The techniques also compensate for patients' cognitive dysfunctions, and each module is a small, self-contained package that can be inexpensively tried and then either rejected or adopted, either alone or in combination with other modules, as the base of a comprehensive rehabilitation program (16, 17).

The purpose of the present research was to confirm that the modules fulfilled their design objectives. If they did, staff would have a set of techniques that they could use to improve the long-term outcomes of their men-

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tally disordered patients by enhancing their community functioning.

## METHOD

### Modules

Each module is a self-contained curriculum that teaches from four to six competencies in a major domain of community functioning. For example, the medication management module teaches five competencies: recognizing medication's benefits, recognizing its side effects, monitoring these side effects, discussing medication with physicians and other caregivers, and recognizing the benefits of injectable medication. Each competency is divided into the specific skills that define the competency and are the focus of the training. For example, competently discussing medication with physicians and other caregivers is divided into pleasantly greeting the physician, describing the problem in detail (including its duration and severity), requesting that action be taken, clarifying and repeating the doctor's prescription, and pleasantly ending the interaction while maintaining appropriate eye contact, posture, and paralinguistic qualities during the entire exchange.

Each competency's constituent skills are taught with the same seven instructional techniques. The first three—introduction, videotape demonstration, role-playing practice—help patients learn and practice the skills in the training sessions. The fourth and fifth techniques—solving resource management problems and solving outcome problems—prepare participants to use their skills outside of the training sessions. The sixth and seventh activities—in vivo exercises and homework assignments—require that participants use the skills outside of the training session. A detailed description of the modules is given elsewhere (16).

Each module consists of a trainer's manual, participant's workbook, and demonstration videotape. The manual specifies exactly what the trainer is to say and do to teach all of the module's skills; the videotape demonstrates the skills; and the workbook provides participants with written material, forms, and exercises that help them learn the skills. The trainer instructs by reading scripts and asking questions written in the manual, by playing the videotape, and by evaluating the participants' role playing with checklists written in the manual. The trainer corrects inaccurate answers or role playing by using prompting, modeling, coaching, and reinforcement. A training session is generally conducted with four to eight patients and one trainer, and sessions are scheduled two or three times per week for 1 to 1-1/2 hours each. Approximately 13 to 20 weeks of twice-weekly sessions are needed to complete each module.

### *Facilities, Staff, and Patients*

Three modules—medication management, recreation, and grooming—were implemented in seven treatment facilities: a long-term rehabilitation program located in a state hospital that treated approximately 200 individuals; five residential care facilities that provided housing for 6, 12, 24, 50, and 60 individuals, respectively; and a day treatment program that treated approximately 35 individuals. The training was conducted by nursing staff in the inpatient program, by the owners/operators of the three smaller residential care facilities, and by recreation therapists and mental health counselors at the two larger residential care facilities and the day treatment program. The trainers' educational and clinical backgrounds ranged from completion of high school to graduation from professional master's degree programs, and from 1 month to 10 years of experience in treating severely mentally ill individuals.

Staff attended a 2-day workshop in which the rationale for each instructional activity was explained and the specific procedures were demonstrated. At the end of the workshop, staff chose the module or modules they would teach, selected the patients, and established a schedule of consultation visits by two experienced research assistants, who had also conducted the workshop.

A total of 126 severely mentally ill patients agreed to participate in training with at least one module; 108 completed the training. The 18 noncompleters were inpatients who were discharged or transferred before the end of training. All 126 had been judged to be deficient in a module's skills and able to participate in the group training sessions. Selection and recruitment were conducted by the facilities' staffs. Approximately 91% of the patients (115 of the 126 recruited and 98 of the 108 completers) had been diagnosed as having a schizophrenic or schizoaffective disorder according to *DSM-III-R* criteria, and most had been hospitalized continuously or episodically for the past several years. The average age of the 108 completers was 33 years (SD= 10), 82 were male, and 81 were Caucasian, nine were black, and 18 were Hispanic.

### *Measures*

Each module's effectiveness in producing its learning objectives was measured by a test that consisted of specific questions and role-playing situations selected from each competency area of the module. The tests were administered by a trained interviewer, who recorded the patients' answers verbatim, classified them as correct or incorrect, and calculated total scores for each competency and for the entire module.

The trainers' competency in teaching was measured by directly observing them and determining the fidelity of their behaviors to those specified in each module's manual. For example, the trainers were observed while conducting a role-playing exercise to determine if they had read the appropriate section from the manual, correctly used the checklist to evaluate each participant's role playing, correctly conducted a group review of the role playing, provided positive feedback, and suggested improvements and conducted a second role-playing exercise if needed. The ratio of performed to specified be-

**TABLE 1. Accuracy and Effectiveness of Module-Based Training in Social and Instrumental Skills for Severely Mentally Ill Patients**

| | | | | Patients' Score | | | |
|---|---|---|---|---|---|---|---|
| | | | | Pretraining | | Posttraining | |
| Site and Skill | Patient Group[a] | N | Percent of Trainer Behaviors That Matched Those Specified in Module Manual | Mean | SD | Mean | SD |
| State hospital | | | | | | | |
| Medication management | Experimental | 7 | 95 | 10.29 | 5.12 | 26.00 | 6.43 |
| | Control | 8 | — | 7.13 | 4.29 | 11.38 | 4.96 |
| Grooming | Experimental | 12 | 96 | 9.92 | 5.82 | 15.75 | 6.92 |
| | Control | 4 | — | 7.77 | 8.34 | 11.00 | 7.53 |
| Day treatment program | | | | | | | |
| Medication management | | 6 | 92 | 14.80 | 3.88 | 28.00 | 1.79 |
| Residential care facilities | | | | | | | |
| Site 1 | | | | | | | |
| Recreation | Experimental | 5 | 83 | 7.30 | 3.44 | 12.57 | 3.01 |
| | Control | 7 | — | 8.40 | 3.62 | 10.60 | 1.51 |
| Grooming | Experimental | 6 | 71 | 12.57 | 3.01 | 22.00 | 4.90 |
| | Control | 7 | — | 12.57 | 4.86 | 14.29 | 7.15 |
| Site 2 | | | | | | | |
| Medication management | Experimental | 7 | 85 | 13.86 | 6.59 | 25.14 | 6.52 |
| | Control | 5 | — | 14.20 | 6.64 | 15.00 | 6.82 |
| Site 3 | | | | | | | |
| Medication management | | 7 | 98 | 14.14 | 5.58 | 23.29 | 5.62 |
| Recreation | | 9 | 70 | 14.44 | 5.66 | 23.44 | 5.38 |
| Site 4 | | | | | | | |
| Medication management | | 5 | 15 | 14.80 | 5.32 | 14.80 | 4.96 |
| Site 5 | | | | | | | |
| Medication management | | 3 | 73 | 10.33 | 3.52 | 17.00 | 10.15 |
| Grooming | | 6 | 71 | 13.00 | 4.15 | 18.00 | 3.03 |

[a] For the programs with relatively few patients, a one-group, pre/post study design was used.

haviors was calculated for each instructional activity, and the results were averaged across all activities to obtain a percentage for each module and facility.

The same research assistants who conducted the staff workshop also administered the tests of accuracy and effectiveness. The tests of effectiveness were administered before the instruction, immediately afterward, and, for the patients remaining at each facility, 1 year later.

In the state hospital program and the two larger residential care facilities a two-group, random-assignment, experimental research design was used; the control group patients were placed on a waiting list. The three smaller residential facilities and the day care program treated relatively few patients, and there a one-group, pre/post, nonexperimental research design was used.

### *Reliability*

Test-retest reliability for each module's measure of effectiveness was determined by calculating a Pearson r for the correlation between the two testings of the control groups at the facilities that used an experimental design. The correlations were 0.87 for the medication management module, 0.64 for the grooming module, and 0.73 for the recreation module.

Interrater reliability for each effectiveness measure was determined by calculating the intraclass correlation coefficient (ICC 2,1 [18, 19]) for the relationship between one research assistant's scoring of the participants' recorded verbatim answers and the scoring of the research assistant who initially administered and scored the test. All information identifying either the patient or the date of the testing was removed from the records of the verbatim answers. The intraclass correlations were 0.94 for the test of the medication management module (N=14), 0.97 for the test of the grooming module (N=20), and 0.95 for the test of the recreation module (N=10).

Several posttraining answers, however, were recitations of the material, which could have informed the second scorer of the date of testing. Hence, the efficacy tests were administered to 10 patients with schizophrenia who were not included in the study, and their performances were videotaped. The tapes were independently scored by the two research assistants, and the intraclass correlations between their scores were 0.92 for the medication management module, 0.97 for the grooming module, and 0.94 for the recreation module.

Interrater reliability of the accuracy measure was determined by calculating the agreement between the two research assistants' independent assessments of 17 training sessions representing all facilities and trainers. The kappa was 0.88.

## RESULTS

### *Short-Term Effectiveness*

Table 1 lists the patients' pre- and posttraining scores for each module and each facility and the percentage of the trainers' behaviors that matched those specified in the modules' manuals averaged across the observations at each facility.

The posttraining scores for the facilities that used an experimental research design were analyzed separately for each module by using a two-way (group, site) factorial analysis of covariance (ANCOVA) for the medication and grooming modules and a one-way (group) ANCOVA for the recreation module with the pretraining scores as the covariate. The results indicated significant differences between the experimental and control groups for each module (medication management: F=26.68, df=1, 22, p<0.0001; grooming: F=7.99, df=1, 24, p=0.009; recreation: F=5.51, df=1, 8, p=0.05). There was no significant difference among the sites (medication: F=0.10, df=1, 22, p=0.76; grooming: F=0.50, df=1, 24, p=0.49) and no significant Site by Group interaction (medication: F=0.44, df=1, 22, p=0.51; grooming: F=1.71, df=1, 24, p=0.20).

To further analyze the effects of training, for each module a partial correlation between the posttraining scores and group was calculated, with partialing of the pretraining scores from both variables. Site was not considered in this analysis since it was not significant either as a main effect or in interaction with group in either the medication or grooming ANCOVA. The results were partial correlations of 0.74 for the medication module, 0.46 for the grooming module, and 0.64 for the recreation module.

To analyze the replicability of each module's effects across treatment facilities, pre/post scores were analyzed with a two-way (site, pre/post) split-plot factorial analysis of variance (ANOVA), one per module. The results indicated that all sources of variance were significant for the medication module: pre/post (F=48.21, df=1, 29, p<0.0001), site (F=2.60, df=5, 29, p=0.05), and the Site by Pre/Post interaction (F=2.91, df=5, 29, p=0.03). The significant interaction was further analyzed with tests of simple main effects; the results indicated that the pre/post differences were significant for all sites except one residential care facility. The posttraining differences among the sites were further analyzed with a one-way ANCOVA using the pretraining scores as the covariate; the differences were significant (F=3.97, df=5, 28, p=0.008). Further analysis using Tukey's honestly significant difference test (corrected for unequal numbers of subjects) indicated that the posttraining scores for two residential care facilities were significantly lower than those for the other sites.

The results of the split-plot factorial ANOVA for the grooming module indicated a significant pre/post main effect (F=106.2, df=1, 21, p<0.0001) and a nonsignificant site main effect (F=1.66, df=2, 29, p=0.21) and Site by Pre/Post interaction (F=3.32, df=2, 29, p=0.06). The results of the split-plot factorial ANOVA for the recreation module indicated a significant pre/post main effect (F=53.03, df=1, 17, p<0.0001), a significant main effect of site (F=11.24, df=2, 17, p=0.0008), and a nonsignificant Site by Pre/Post interaction (F=2.85, df=2, 17, p=0.09). Further analysis using Tukey's honestly significant difference test (corrected for unequal numbers of subjects) indicated that the scores at one residential care facility were significantly higher overall than at the other sites. This was confirmed by a one-way ANCOVA of the differences among the sites using the pretraining scores as the covariate; the main effect of site was significant (F=4.48, df=2, 16, p=0.03) because the scores at one residential care facility were higher than the scores at the other two sites.

### *Long-Term Effectiveness*

The participants who remained at the facilities 1 year later and to whom the follow-up tests were administered (N=35) did not differ significantly in age, sex, ethnicity, or hospitalization from the complete set of participants. The data were analyzed with a one-way ANOVA for repeated measures, followed by a Tukey's honestly significant difference test for significant main effects. The results indicated that for all three modules there were significant improvements from pre- to posttraining that had not declined at the follow-up testing.

### *Accuracy of Instruction*

As indicated in table 1, except for the residential care facility that did not achieve a learning effect, the trainers' behaviors substantially matched those specified in the manuals.

## DISCUSSION

The results confirm that the modules fulfilled their design objectives; with only a modicum of training and ongoing consultation, staff from diverse clinical and educational backgrounds working in diverse treatment facilities accurately taught the modules and achieved significant increases in the patients' knowledge and performance of the skills targeted by the training. This study replicates and considerably extends—with a more rigorous design and more modules—the previously reported findings on the modules in a national field test of 28 mental health facilities (20). Not only did the modules achieve their effects in both studies within the constraints of typical facilities that treat severely mentally ill patients, but the confirmation of the modules' effects in this study was achieved with both nonexperimental and experimental research designs, the latter of which showed significant effects with the medication and grooming modules in two facilities.

The results with the experimental design indicated that the size of the modules' effects ranged from moderate to substantial; the percentages of shared common variance between the posttraining scores and the group variable after partialing the pretraining scores were 54.9% for the medication module, 40.8% for the recreation module, and 21.3% for the grooming module. These immediate effects were not restricted to the more functional patients; although the more dysfunctional and regressed inpatients had lower pre- and posttraining scores, their changes were not significantly different from those of the other patients. Furthermore, these effects were maintained over a 1-year follow-up, which is noteworthy given that functioning deficits tend to endure in spite of improvements in symptoms (21).

The results, however, point to the limitations of the modules. In spite of the modules' robust effects, they certainly did not produce a perfect learning outcome for every patient who participated in the training. Unfortunately, to fulfill the research objectives of this study, the training was conducted for standardized durations at all sites regardless of the patients' performance. A clinically more satisfactory approach may be to conduct the instruction for each module on a "mastery" basis, i.e, conduct training until each patient achieves 100% correct. However, given the relatively poor posttraining scores of the inpatients in particular—despite their having achieved substantial learning—mastery training might require extensive and time-consuming repetitions of a module. Perhaps this is to be expected given the chronic nature of the patients' illnesses and the many years that have elapsed since most were exposed to learning in a classroom environment.

The results from one residential facility also indicate that extensive deviations from the specified procedures can be deleterious. The facility's trainer eliminated several learning activities and changed the content and order of the remaining ones. Not surprisingly, the participants' knowledge and performance of the module's skills did not improve.

The results did not address the effects of the modules on global clinical outcomes, such as relapse and rehospitalization. Since the modules are specifically designed as encapsulated units whose content, form, and size allow each to be easily adapted to the structure of diverse treatment settings, they are not meant as a comprehensive system of care that will change global clinical outcomes. Rather, since each addresses a major domain of social and instrumental functioning, the set of them can form the cornerstone of a comprehensive system of care that encompasses the pharmacotherapy, vocational, family, case management, and individual services needed to rehabilitate persons with long-term mental illness. Controlled clinical evaluations of the set of modules, embedded in a comprehensive system of care, are currently underway (22).

The national plans for schizophrenia and services research (23, 24) include a recommendation for design of skill-building treatments that are relevant to the real world of clinical programs and produce durable improvements in functioning and independence. As Lehman (25) noted in a description of the current and contemplated changes in the political and funding arrangements for services to severely mentally ill patients, new arrangements will be successful only if they include effective treatments that are operationalized by skilled and motivated clinicians. The results of this study indicate that the modules are easily used, effective, and highly focused services that clinicians can profitably add to their armamentarium of clinical tactics.

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# Changes in Chronic Nightmares After One Session of Desensitization or Rehearsal Instructions

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*Objective: The purpose of this study was to examine the effects of one session of instructions on the frequency of chronic nightmares and on self-rated distress. Method: Twenty-eight volunteers with chronic nightmares (mean duration=19 years) were treated with either one session of desensitization with instructions on how to practice this treatment or with one session of instructions to change the nightmare and how to rehearse the new version. The authors administered four scales of the SCL-90 and the corresponding scales of the Symptom Questionnaire. Results: At 7-month follow-up of 23 patients, there was a significant reduction in the frequency of nightmares and significant decreases in self-rated depression, anxiety, and hostility. There were no significant differences between the effects of the two types of treatment. In four patients, whose mean duration of nightmares was 23 years, the nightmares ceased. Conclusions: The results of this preliminary study suggest that the instructions given to the patients reduced the frequency of their chronic nightmares and decreased their self-rated distress.*

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Several methods have been proposed for the treatment of chronic nightmares, including rehearsal and desensitization. Halliday (1) cited several case studies in which rehearsal was used effectively to treat nightmares. Marks (2) described a patient with chronic nightmares who was treated successfully with rehearsal after she imagined a triumphant ending of the nightmare. Bishay (3) described seven patients treated with rehearsal and an altered ending. In a previous uncontrolled study (4), we treated four patients who had chronic nightmares. The patients had one session consisting of instructions on how to rehearse the nightmare and how to imagine a different ending; in three of the patients, the nightmares abruptly ceased.

There are two published controlled studies on the treatment of nightmares, and in both the treatment consisted of desensitization (5). Cellucci and Lawrence (6) and Miller and DiPilato (7) found that the outcome of patients given five or six sessions of desensitization was significantly better than that of untreated control subjects. To our knowledge, there are no published controlled studies of rehearsal.

The present study is one of a series of experiments in the treatment of chronic nightmares. Our aims were to examine the effects of one session of instructions on how to rehearse the nightmare, to use a group setting instead of treating individuals separately, and to compare the effects of rehearsal with those of desensitization.

## METHOD

Advertisements and articles in local news media recruited adults 18 years or older who had suffered from recurrent nightmares for 6 months or longer. Sixty-two callers were interviewed by telephone to determine whether they were suitable for the study. Callers who were abusing alcohol or other drugs were excluded; the rest were invited for an intake interview to determine whether any suffered from psychosis or organic brain syndrome, which would have been grounds for exclusion. No attempts were made to contact patients who failed to attend the intake interview.

### *Subjects*

Thirty-six subjects met our criteria and agreed to participate after the nature of the study had been explained. All met *DSM-III-R* criteria for the diagnosis of dream anxiety disorder (nightmare disorder) (307.47). Seven subjects who participated in the intake interview failed to attend their treatment session for reasons such

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as illness or deciding not to participate; one subject was excluded from the study because the nightmares were apparently caused by antiparkinsonian drugs. The remaining 28 subjects were assigned at random to either rehearsal (N=14) or desensitization (N=14). One patient who completed treatment in each group could not be reached for follow-up. Another patient could not be contacted at 4 months, and two could not be contacted at 7 months.

The mean age of the patients treated with desensitization was 48 years (SD=14.9); the mean age of the patients treated with rehearsal was 36 years (SD=12.5) (t=2.1, df=23, p<0.04). There were no significant differences between the groups on any of the other measures. For the 26 patients who completed treatment and were followed up the duration of the disorder ranged from 2 to 46 years (mean=20.6 [SD=14.6]). The median frequency was 2–3 nightmares a week. Except for one patient who had an average of 2–3 nightmares a month during the preceding 6 months, all others had nightmares at least once a week.

Nineteen patients were women and seven were men. Twenty-two were Caucasian and the remainder were black, Native American, or Oriental. Seventeen were married. Their socioeconomic classes were similar to those of the city's population.

One patient, a 53-year-old woman, was being treated with 200 mg/day of amitriptyline for a coexisting depression when she entered the study; her nightmares had preceded the taking of the drug by several years and did not change after she started taking the drug. None of the other patients took hypnotics or psychotropic drugs, and there was no evidence that organic factors caused the chronic nightmares.

### Procedures

The protocol was approved by the research committees of the medical school. The intake interview consisted of taking a medical and psychiatric history as well as a detailed history of the nightmares. The purpose of the study and the procedures were explained to the patients and the patients were asked to give oral and written consent. The interviewing psychiatrist rated the frequency of the nightmares and administered self-rating scales. The patients were assigned to a 1–2-month waiting list, and during this period they were asked to record and describe their nightmares in a diary.

We used the following outcome criteria: 1) a 5-point rating scale of frequency of nightmares during the past month on which 1=not at all, 2=one or two times a month, 3=once a week, 4=two or three times a week, and 5=four or more times a week, 2) a 4-point global rating scale of intensity of emotional symptoms (fear, terror, panic, etc.) during the nightmare and symptoms on awakening on which 3=severe and 0=no symptoms, 3) the same scale for the rating of bodily symptoms (heart racing, breathlessness, sweating, etc.), 4) self-rating scales of anxiety, depression, hostility, and somatic symptoms of the SCL-90 (8), and 5) the Symptom Questionnaire (9), which contains the same four scales. The last two scales are scored differently and have somewhat different psychometric properties. We administered both as a method of cross-validation of the results.

We intended initially to rely entirely on self-rating scales and on daily diaries of nightmares completed by the patients as outcome measures. Only 16 patients (eight in each group), however, kept adequate diaries after the initial visit. We decided, therefore, to use as outcome measures the rating of frequency of nightmares and self-ratings of the SCL-90 and Symptom Questionnaire. In the 16 patients the recorded frequencies of nightmares in the diaries were congruent with the 5-point-scale frequency ratings.

### Treatments

Both treatments were carried out by the same psychiatrist (J.N.). Except for two patients who could not keep their appointments for the treatment session and who were treated individually, the rest were treated in groups of two to five patients. Both treatments consisted of one session with instructions on how to practice the treatment at home.

*Desensitization with muscular relaxation.* This treatment is based on Wolpe's method of reciprocal inhibition (5). Each patient was given an instruction booklet describing a modified form of progressive relaxation with desensitization (10). The patients were told to write down their nightmares. They were also told how to practice muscular relaxation during the first week and instructed to imagine the nightmare, to relax whenever the imagined nightmare caused any tension, and to practice relaxation before falling asleep during the second and third weeks. The patients were told to practice once a week during the fourth through eighth weeks but to do so more often if the nightmares persisted.

*Rehearsal of changed nightmare.* In this treatment, the patients were told to 1) select a recent nightmare and write it down, 2) change the nightmare any way they wished, 3) write down the changed version, and 4) rehearse the changed nightmare in imagery in a relaxed state. After doing so, they repeated the same steps during the same session without the therapist's guidance. Patients were told to rehearse each changed version once a day for 3 consecutive days after each nightmare or until the nightmares went away. They were given a two-page instruction sheet on the procedures.

Patients in both treatment groups were encouraged to telephone if they encountered any problems. Three patients telephoned once and one patient telephoned twice.

### Follow-Up

After 4 months, the patients were contacted by telephone and responded to a nightmare questionnaire; the ratings of the frequency and severity of the nightmares were based on the patients' replies. The interview was conducted by the psychiatrist who carried out the initial ratings. At 7 months this procedure was repeated. Telephone calls were limited to 10 minutes. At 7 months the patients were also mailed the SCL-90 and the Symptom Questionnaire and asked to fill them in and mail them back in a self-addressed stamped envelope.

The seven patients who participated in the intake interview but did not receive treatment were contacted by telephone after 7 months. They responded to the same nightmare questionnaire as the treated patients.

### *Statistical Analysis*

Changes over time within each group and across both groups, as well as between-group comparisons of the SCL-90 and Symptom Questionnaire scale scores, were tested by using two-response repeated-measures analysis of variance (ANOVA) (11). This procedure allowed for simultaneous testing of change over time, between-group comparisons, and presence of interaction between the group and time effects. If interaction was observed, the groups were then analyzed separately by using a paired t test. For the analysis of frequency of nightmares and the severity of bodily and emotional symptoms, the same approach was used but with three-response repeated-measures ANOVA because these variables were recorded at pretreatment, at 4-month follow-up, and at 7-month follow-up. All statistical analyses were carried out by using the repeated-measures ANOVA procedure or the paired t test procedure in the SAS statistical package for personal computers (12).

## RESULTS

### *Recovered Patients*

For four patients, whose mean duration of nightmares was 23 years, the nightmares ceased completely.

A 34-year-old woman had had nightmares four or more times a week since the age of 4 years. After practicing rehearsal for 3 days the nightmares ceased. She was ecstatic; she said that this had changed her life.

A 58-year-old woman had had nightmares four or more times a week for 5.5 years. After 3 months of rehearsal the nightmares ceased. "I am getting a restful sleep, I do not remember dreaming."

A 40-year-old woman had had nightmares about 2 to 3 times a week for 13 years. The nightmares ceased after practicing desensitization for 3–4 weeks. "I have a peaceful sleep and I am no longer afraid to go to sleep."

A 68-year-old man had had nightmares about once a week for 46 years. The nightmares decreased substantially after 1 month and ceased after 3 months. He continued to practice relaxation.

### *Changes in the Two Groups*

In the 16 patients who completed daily nightmare diaries while awaiting treatment, there was no change in the frequency of nightmares before treatment. After treatment, the frequency of nightmares decreased significantly in both groups. The mean score for the frequency rating for nightmares (see Procedures section) in the rehearsal group decreased from 4.4 (SD=0.8) to 3.3 (SD=1.5) at 4 months and 2.2 (SD=1.3) at 7 months. In the desensitization group the mean frequency rating for nightmares decreased from 4.2 (SD=1.2) to 2.7 (SD=1.4) at 4 months and 2.6 (SD=1.4) at 7 months. According to the three-response repeated-measures ANOVA the change across both groups was significant at 4 months (F=16.2, df=1, 21, $p<0.0006$) and at 7 months (F=33.8, df=1, 21, $p<0.0001$). There were no significant differences between the two groups in the changes in the frequency of nightmares.

At 7 months the mean rating of the severity of emotional symptoms experienced during the nightmare and on awakening had decreased in the desensitization group from 2.7 (SD=0.5) to 1.4 (SD=1.0) (t=–4.33, df=9, $p<0.002$, paired t test). The corresponding decrease in the rehearsal group was from 2.7 (SD=0.5) to 2.3 (SD=0.9) (t=–1.5, df=9, n.s., paired t test). Decreases in bodily symptoms were not significant in either group.

Self-ratings on all scales of the SCL-90 and the Symptom Questionnaire decreased from pretreatment to the end of follow-up for both treatments. Depression, anxiety, and hostility scores decreased significantly in both groups on the SCL-90 as well as on the Symptom Questionnaire; the changes on the somatic scales were not significant. The significance levels tended to vary with the scales (table 1).

None of the treated patients reported an increase in the frequency of nightmares. Two patients (one in each group) reported a decrease in frequency but an increase in severity of the nightmares.

Of the seven subjects who participated in the intake interview but received no treatment, two experienced no change in the frequency of nightmares and two experienced nightmares more often. Three of these subjects experienced a decrease in nightmare frequency: one was recording her nightmare, one obtained psychiatric treatment as an inpatient, and one had learned a yoga-type of relaxation and practiced desensitization on her own.

## DISCUSSION

The frequency of nightmares decreased significantly 7 months after one treatment in 23 patients who had experienced nightmares for an average of more than 20 years. These patients' self-ratings of depression, anxiety, and hostility but not of somatic symptoms significantly improved. There were no significant differences between the groups who were treated with rehearsal and those who were treated with desensitization. The patients' mean self-ratings on the SCL-90 and the Symptom Questionnaire for depression, anxiety, hostility, and somatization were in the range of psychiatric outpatients before treatment and approached the means of family practice and medical patients after treatment (13–15).

**TABLE 1. Changes in the Scores of 23 Patients With Chronic Nightmares[a] on the Anxiety, Depression, Somatization, and Hostility Subscales of the SCL-90 and the Symptom Questionnaire After One Session of Desensitization or Rehearsal Instructions**

| | Desensitization Group | | | | | Rehearsal Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before Treatment | | 7-Month Follow-Up | | | Before Treatment | | 7-Month Follow-Up | | | | |
| Scale | N | Mean | SD | Mean | SD | N | Mean | SD | Mean | SD | F[b] | df | p |
| Anxiety | | | | | | | | | | | | | |
| SCL-90 | 11 | 1.4 | 0.9 | 0.8 | 0.7 | 10 | 1.4 | 0.7 | 0.8 | 0.5 | 16.5 | 1, 19 | 0.001 |
| Symptom Questionnaire | 12 | 13.8 | 5.6 | 9.3 | 8.3 | 9 | 16.6 | 6.1 | 10.7 | 6.0 | 7.9 | 1, 19 | 0.01 |
| Depression | | | | | | | | | | | | | |
| SCL-90 | 11 | 1.8 | 0.9 | 0.9 | 0.9 | 10 | 1.9 | 0.5 | 1.2 | 0.7 | 20.1 | 1, 19 | 0.001 |
| Symptom Questionnaire | 10 | 12.1 | 6.8 | 5.5 | 6.6 | 10 | 14.9 | 4.4 | 8.1 | 6.3 | 18.4 | 1, 18 | 0.001 |
| Somatization | | | | | | | | | | | | | |
| SCL-90 | 11 | 1.1 | 0.7 | 0.9 | 1.0 | 10 | 0.7 | 0.3 | 0.5 | 0.3 | 1.9 | 1, 19 | n.s. |
| Symptom Questionnaire | 11 | 8.7 | 4.2 | 7.7 | 5.6 | 10 | 9.0 | 3.8 | 7.6 | 4.7 | 0.9 | 1, 19 | n.s. |
| Hostility | | | | | | | | | | | | | |
| SCL-90 | 11 | 1.0 | 0.8 | 0.6 | 0.5 | 10 | 0.9 | 0.6 | 0.4 | 0.3 | 15.2 | 1, 19 | 0.001 |
| Symptom Questionnaire | 11 | 9.6 | 5.1 | 7.4 | 6.7 | 9 | 15.1 | 6.7 | 8.6 | 4.5 | 7.2 | 1, 18 | 0.05 |
| Total | | | | | | | | | | | | | |
| SCL-90 | 11 | 1.4 | 0.7 | 0.8 | 0.8 | 10 | 1.3 | 0.4 | 0.8 | 0.4 | 18.4 | 1, 19 | 0.001 |
| Symptom Questionnaire | 10 | 43.2 | 15.7 | 26.2 | 23.6 | 8 | 58.8 | 14.9 | 36.9 | 15.9 | 11.5 | 1, 18 | 0.005 |

[a] Fourteen subjects in each group completed the treatment. One patient in each group could not be reached for any follow-up. Another patient could not be contacted at 4 months, and two could not be contacted at 7 months. A few patients did not return the self-rating scales or returned incomplete scales. N indicates the number of complete scales.

[b] Repeated-measures ANOVA for the before-after treatment comparison across both groups. No statistically significant differences were observed between the effects of the two treatment groups. The test for interactions was not significant.

The seven patients who did not receive the treatment in the present study cannot be regarded as a random untreated control group. It is of interest, however, that none of the patients in the treated groups failed to improve to some degree but two of the seven untreated patients remained unchanged and two got worse. Of the three untreated patients who improved, one rehearsed the nightmares by recording them and two were exposed to some form of treatment.

At present we are conducting a study of a group of patients given one session of rehearsal compared with a control group of subjects who are recording their nightmares in a diary. The findings suggest that the effects of rehearsing the changed nightmare are similar to those of the present study.

Our finding of a reduction in nightmares after one session of treatment in the present study is comparable to findings of two previous controlled studies in which the patients were treated with five or six sessions of systematic desensitization. Whether more elaborate treatments will improve results is unknown; one session, however, appears to constitute adequate treatment for some patients.

An altered, favorable, or triumphant ending of the nightmare is not essential for improvement or recovery. The patients in the desensitization group improved and yet had not changed the ending of their nightmares. Both groups had rehearsal in common (one of a changed version, the other of the original nightmare), which is a form of exposure. The treatment of phobias with exposure takes several sessions and leads to gradual and intermittent improvement, but rehearsal, in a few patients, has resulted in rapid recovery from chronic nightmares without recurrences.

The interpretation of dreams has been one of the tenets of Freudian psychoanalytic theory. In our study we compared simple treatments and did not attempt to deal with the psychodynamics of the patients' nightmares. Chronic nightmares and recurring dreams of a traumatic event have been described in posttraumatic stress disorder (PTSD) in children and in adults (*DSM-III-R*, pp. 248–249). In the present study we elicited detailed histories from the patients but did not explore specifically whether psychological trauma preceded the onset of nightmares. Discussions of the psychodynamic implications and the relationship of chronic nightmares to PTSD lie beyond the scope of this report.

The reason for the decrease in the frequency of nightmares is not known. It may have been in part a spontaneous improvement with the passage of time, in part a placebo effect ("the impact of a place of healing" [16, 17]), or the effect of exposure to the nightmares in the waking state. The extent to which these factors contributed to the observed improvement is at present unknown. These results must be regarded as preliminary and require replication.

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# Posttraumatic Stress Disorder Among Substance Users From the General Population

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*Objective: The purpose of the study was to evaluate the prevalence of posttraumatic stress disorder (PTSD) among substance users in the general population. Method: The St. Louis Epidemiologic Catchment Area study, a survey of psychiatric illness in the general population, collected data on PTSD and substance use with the Diagnostic Interview Schedule. Among the 2,663 respondents, 430 reported a traumatic event that could qualify for PTSD; however, the rate of PTSD was low, 1.35% overall. To evaluate the relationship between PTSD and substance use, respondents were hierarchically classified into one of four substance use categories ranging from polydrug use to alcohol use only. Substance users from each category as well as substance users in general were compared with persons who did not meet the substance use threshold (comparison subjects). Results: Findings indicate that cocaine/opiate users are over three times as likely as comparison subjects to report a traumatic event, report more symptoms and events, and are more likely to meet diagnostic criteria for PTSD. Physical attack, but not combat-related events, was the most prevalent event reported among cocaine/opiate users. Onset of substance use preceded onset of posttraumatic symptoms, suggesting that substance use predisposes the individual to exposure to traumatic events. When other variables—including antisocial behavior—were controlled, female gender and use of cocaine/opiates predicted PTSD. Conclusions: These analyses of the co-occurrence of substance abuse and PTSD warrant further study and suggest that PTSD is much more common among substance abusers than was previously known.*

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Several studies have suggested a strong relationship between substance use and posttraumatic stress disorder (PTSD). For example, a report by Helzer et al. (1) from the St. Louis National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) project, a multistage probability survey of psychiatric illness in the general population, reveals that men with PTSD were five times as likely as men without PTSD to have a *DSM-III* drug abuse or dependence disorder; women with PTSD were 1.4 times as likely to have drug abuse or dependence as women without PTSD. In a study of postdisaster victims, Smith et al. (2) found that 22% of subjects with PTSD had been abusing or were dependent on alcohol before the disaster. In addition, Breslau and Davis (3) found the rate of drug abuse or dependence to be 86% among Vietnam veterans with PTSD. The relationship between PTSD and substance use is of concern since psychoactive substance use may increase the risk of exposure to events outside the range of normal experience, which in turn may increase the risk for experiencing symptoms of PTSD. Moreover, little is known about risk factors for PTSD in the general population. To address these salient issues, we have expanded analyses on PTSD by using data from the St. Louis ECA sample.

The ECA sample is an especially useful sample for such an evaluation because selection of these general population subjects was not based on substance use, PTSD, or experience in the combat theater of war. Moreover, the sample includes women, who are rarely studied. The questions addressed in this evaluation included the following: 1) Are substance users at greater risk for traumatic events than are nonusers? 2) Do substance users experience certain events more often than nonusers? 3) Once exposed to an event, are substance users more likely than nonusers to meet the criteria for

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PTSD? 4) Are certain substance use patterns associated with greater risk for PTSD than others? 5) Do symptom patterns among those who experienced an event vary with type of substance? 6) Does the onset of drug abuse precede the onset of symptoms attributable to a traumatic event? 7) When other risk factors are controlled, which variables best predict PTSD?

## METHOD

### *Sample*

The data for these analyses were collected in 1982 and 1983 as part of the second wave of the St. Louis NIMH ECA survey (4), a study of the lifetime prevalence and 1-year incidence of mental disorders in the general population. (Five sites nationwide were selected to participate in this study of approximately 20,000 respondents; however, since questions to assess the *DSM-III* diagnosis of PTSD were not included in the "core" psychiatric interview used at other sites, only the data from the St. Louis site are available for these analyses.) The NIMH Diagnostic Interview Schedule (DIS), a structured interview that can be administered by trained nonclinician interviewers, was used as the core psychiatric interview to obtain the information necessary to make psychiatric diagnoses (5). The DIS has been shown to have very good reliability for substance abuse disorders (6) and PTSD (3).

From the St. Louis site 3,004 household residents were interviewed in the first wave. Individuals were selected after a five-stage probability sampling that began with selection of three mental health catchment areas. These three were selected for this general population study because they approximated the demographic composition of the nation as a whole in 1980, and thus the results would allow for the generalizability of findings to other U.S. communities. After the catchment area was selected, census tracts, enumeration districts, blocks, and households were selected. An 81% overall completion rate for the first wave was achieved (7).

One year later, the same respondents were asked to participate in a follow-up interview. At that time, questions to assess *DSM-III* PTSD were added. All data for this paper came from persons who continued to participate in the second wave of the study, that is, participants in the 1-year follow-up. However, when age at onset of drug use is compared with age at first PTSD symptom, the first wave data are used because this information was not elicited again at the second wave. The sample size was 2,663, representing an 89% one-year follow-up rate.

### *Substance Abuse Questions*

Lifetime history of substance use was obtained by the DIS. As part of the DIS, respondents were given a list of the names of psychoactive medications and asked which they had used more than five times in their life without a prescription, more than prescribed, or to get high. On the basis of their self-reported drug use, respondents were classified into one of five mutually exclusive substance use groups for these analyses. Briefly, 1) cocaine/opiate users were those persons who ever used heroin, other opiates, or cocaine (whether or not they used other drugs); 2) pill/hallucinogen users were those who reported using amphetamines, barbiturates, tranquilizers, or hallucinogens regardless of manner of administration and may or may not have used marijuana and alcohol; 3) users were classified in the marijuana category if their substance use was restricted to cannabinoids, with or without alcohol; and 4) the heavy alcohol category was reserved for persons whose substance use was limited to drinking heavily once a week for at least 2 months or persons who met criteria for alcohol abuse or dependence. A residual category of nonusers consisted of all persons who did not meet the thresholds for use as previously defined and represent the comparison group. These mutually exclusive categories have provided a useful hierarchy with which to make comparisons (8). This classification of substances relies heavily on prior work which shows that marijuana is a "gateway" drug; therefore, those who limit their drug use to marijuana may have different vulnerabilities to stress. In addition, prior studies have shown that a history of heroin use is associated with other substance use (9–11). These same studies have also found that pill users form another group with different problems and consequences of drug use. The substance use classification employed in the present analyses has been previously associated with high-risk sexual behaviors (12).

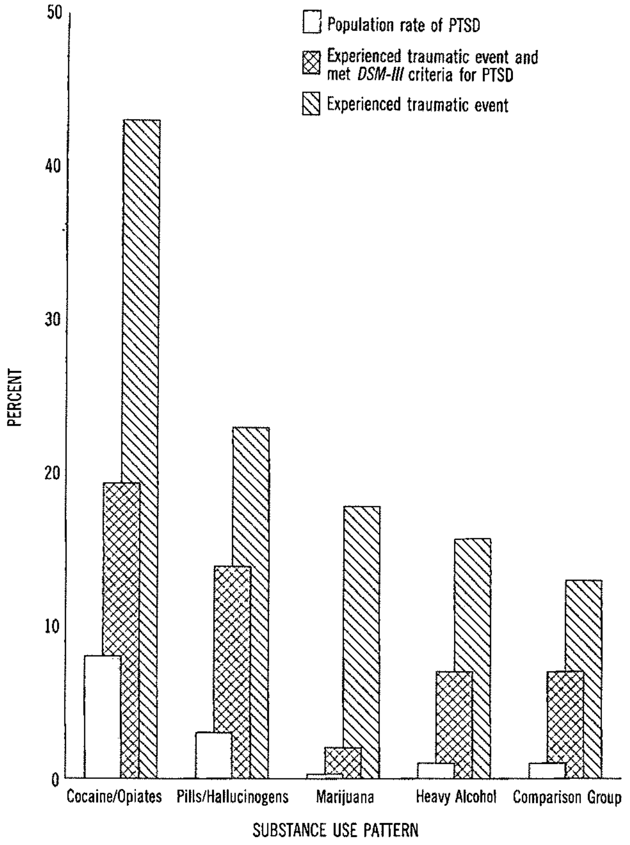
### *PTSD Questions*

The DIS was also the instrument used to assess the *DSM-III* diagnosis of PTSD. Respondents were asked whether they had ever experienced something so horrible that they had nightmares from it. If so, they were asked an open-ended question about the nature of the event. The categories of events included combat, serious accident, physical attack, natural disaster, threats, witnessing someone being killed or injured, and a category for other. The respondents were then asked whether they had jumpiness, guardedness, insomnia, trouble concentrating, social impairment, or loss of interest after that particular event or after any other event outside the normal range of human experience. Responses regarding two additional symptoms, being ashamed after such an event and avoiding situations that reminded them of the event, were also elicited. Thus, the DIS version III PTSD section focused not on event-related symptoms but on symptom-related events. Responses regarding onset of the event-induced symptom, as well as duration and recency of the symptom, were also elicited.

### *Data Analysis*

Associations found between substance use and PTSD were tested by using the chi-square statistic, with one degree of freedom, in the following instances: 1) when sub-

**FIGURE 1. Traumatic Events and PTSD Among Substance Users and Comparison Subjects[a]**



[a]St. Louis Epidemiologic Catchment Area data.

stance users as a group were contrasted with comparison subjects and 2) when each substance use group was contrasted with the comparison group. Odds ratios and their 95% confidence intervals were calculated by using the Epistat program for the personal computer. The Bonferroni correction, a more conservative test that takes into consideration the number of substance category comparisons (N=4), was also used. With the Bonferroni test, each p value is multiplied by 4 before statistical significance is assessed. Both Bonferroni-adjusted p values and unadjusted confidence intervals are given. To test the difference between means of each substance use group and the comparison group mean, the Dunnett test was performed (13). Logistic regression in personal computer SAS version 6.04 was used to evaluate risk factors for exposure to traumatic events and was used separately to evaluate vulnerability to PTSD among subjects exposed to events, while the effects of other variables were controlled.

## RESULTS

### *Demographics of the Sample*

The sample for these analyses consisted of 1,094 men and 1,569 women. At the time of the second wave, the youngest respondents were at least 19 years of age. The mean age of the sample was 43.6 years (SD=19); 38% of the sample was black, which represents an oversample of this population in St. Louis.

### *Prevalence of Substance Abuse and Posttraumatic Stress*

The data from the 2,663 respondents indicate that 144 persons (5%) reported lifetime cocaine/opiate use, 163 (6%) reported pill/hallucinogen use, 308 (12%) reported marijuana only use, and 388 (15%) reported heavy or problem drinking. The remaining 1,655 persons (62%) did not meet the defined thresholds for any substance use and were classified as comparison subjects. (Data were missing for five subjects.) Thus, 38% of the sample met the criteria for substance use.

Overall, 430 persons (16%) reported ever experiencing a symptom-related event. The lifetime prevalence of *DSM-III* PTSD in this general population sample was 1.35%.

### *Associations*

Substance users experienced more traumatic events than nonusers (odds ratio=1.83, 95% confidence interval=1.47–2.26). Moreover, there was an increasing relationship between use of the more addictive illicit drugs and reports of traumatic events. As shown in figure 1, 43% of the polydrug or cocaine/opiate users reported experiencing a qualifying PTSD event, compared with 23% of the pill/hallucinogen users, 18% of the marijuana users, 16% of the heavy alcohol users, and 13% of the comparison subjects. Cocaine/opiate users were statistically significantly more likely than comparison subjects to report a qualifying event (odds ratio=5.06, 95% confidence interval=3.48–7.37), as were pill/hallucinogen users (odds ratio=1.95, 95% confidence interval=1.29–2.94) and marijuana users (odds ratio=1.46, 95% confidence interval=1.04–2.04) but not alcoholics.

Substance users, in general, were not more likely than comparison subjects to experience certain types of stressors. However, when specific substances were evaluated, physical attack was the event most likely to be reported by cocaine/opiate users (table 1). In fact, cocaine/opiate users were over three times as likely as comparison subjects to experience a physical attack. Combat-related events were ranked among the least prevalent events reported by cocaine/opiate users and were no more likely to occur among substance abusers than nonusers, except for the heavy alcohol group. These persons were over three times as likely to have experienced combat-related events. All other stressors were as likely to occur among comparison subjects as among substance users.

Among the subjects exposed to events, cocaine/opiate users were more likely than comparison subjects to meet *DSM-III* criteria for PTSD (odds ratio=3.62, 95% confidence interval=1.46–8.94). Denominators for

**TABLE 1. Types of Traumatic Events Reported by Substance Users and Comparison Subjects Who Experienced an Event**

| | Cocaine/ Opiates (N=62) | | Pills/ Hallucinogens (N=36) | | Marijuana (N=55) | | Heavy Alcohol (N=61) | | Comparison Subjects (N=215) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event[a] | N | % | N | % | N | % | N | % | N | % |
| Combat | 9 | 15 | 4 | 11 | 3 | 5 | 15 | 25[b] | 18 | 8 |
| Serious accident | 7 | 11 | 6 | 16 | 9 | 16 | 8 | 13 | 28 | 13 |
| Physical attack | 21 | 34[c] | 5 | 14 | 8 | 15 | 12 | 20 | 30 | 14 |
| Witness to killing or injury | 16 | 26 | 7 | 19 | 15 | 28 | 15 | 25 | 56 | 26 |
| Trauma | 19 | 31 | 12 | 32 | 10 | 18 | 11 | 18 | 64 | 30 |
| Threat | 13 | 21 | 11 | 30 | 14 | 25 | 12 | 20 | 52 | 24 |

[a] Disaster was excluded because the overall prevalence was low (N=8, 1.86%).
[b] Odds ratio=3.57, 95% confidence interval=1.57–8.11, Bonferroni p=0.005; referent category is comparison subjects.
[c] Odds ratio=3.16, 95% confidence interval=1.56–6.37, Bonferroni p=0.004; referent category is comparison subjects.

**TABLE 2. PTSD Symptoms Among Substance Users and Comparison Subjects Who Experienced Traumatic Events**

| | Cocaine/ Opiates (N=62) | | Pills/ Hallucinogens (N=36) | | Marijuana (N=55) | | Heavy Alcohol (N=61) | | Comparison Subjects (N=215) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event | N | % | N | % | N | % | N | % | N | % |
| Nightmares | 28 | 45 | 17 | 47 | 25 | 45 | 27 | 44 | 89 | 41 |
| Jumpiness | 35 | 56 | 18 | 50 | 25 | 45 | 35 | 57 | 94 | 44 |
| Guardedness | 27 | 44[a] | 9 | 25 | 14 | 25 | 15 | 25 | 56 | 26 |
| Sleep problems | 34 | 55[b] | 15 | 42 | 16 | 29 | 18 | 30 | 81 | 38 |
| Trouble concentrating | 20 | 32 | 13 | 36 | 12 | 22 | 13 | 21 | 56 | 26 |
| Social impairment | 18 | 29[c] | 9 | 25 | 2 | 4 | 5 | 8 | 28 | 13 |
| Loss of interest | 18 | 29[d] | 5 | 14 | 7 | 13 | 8 | 13 | 35 | 16 |
| Ashamed | 9 | 15 | 5 | 14 | 1 | 2 | 0 | 0 | 10 | 5 |
| Avoidance | 16 | 26 | 13 | 36 | 10 | 18 | 7 | 11[e] | 52 | 24 |

[a] Odds ratio=2.19, 95% confidence interval=1.16–4.11, Bonferroni p=0.05; referent category is comparison subjects.
[b] Odds ratio=2.00, 95% confidence interval=1.09–3.70, Bonferroni p=0.09; referent category is comparison subjects.
[c] Odds ratio=2.73, 95% confidence interval=1.31–5.66, Bonferroni p=0.02; referent category is comparison subjects.
[d] Odds ratio=2.10, 95% confidence interval=1.03–4.26, Bonferroni p=0.16; referent category is comparison subjects.
[e] Odds ratio=0.41, 95% confidence interval=0.15–0.99, Bonferroni p=0.20; referent category is comparison subjects.

rates of PTSD have previously included all persons whether or not they have been exposed to an event. This may have produced underestimates of the rates. Our analyses evaluated the rate of PTSD among persons who were at risk because they had been exposed to an event. Thus, we feel these rates are more appropriate and closer to the true prevalence rates. As shown in the middle row of figure 1, nearly one-fifth of the cocaine/opiate users exposed to events met criteria for PTSD (19%); thus, the higher exposure to events among these persons was associated with a concomitant higher rate of PTSD. The rate of PTSD among the persons experiencing an event was lowest among persons whose illicit substance use was limited to marijuana (2%). Surprisingly, the event-exposed marijuana users were less likely to meet criteria for PTSD than were comparison subjects exposed to events (odds ratio=.27, 95% confidence interval=0.02–2.10). Although not statistically different from the rate among comparison subjects, the lower rate among marijuana users is noteworthy, since the rate of exposure to events among marijuana users was not similarly lower than that of all other substance use groups.

The overall rate of PTSD among persons regardless of event exposure was higher among substance users than comparison subjects (odds ratio=2.63, 95% confidence interval=1.28–5.43). Shown in the first row of bars in figure 1 are general population rates of PTSD among persons regardless of exposure to an event. The general population lifetime prevalence rates of PTSD were 8.3% among cocaine/opiate users and 0.3% among comparison subjects. Persons whose drug use patterns included cocaine or opiates were over 10 times as likely as comparison subjects to meet criteria for PTSD (odds ratio=10.75, 95% confidence interval=4.56–25.25). Persons with a pattern of pill and/or hallucinogen use, regardless of event exposure, were almost four times as likely as comparison subjects to meet criteria for PTSD (odds ratio=3.68, 95% confidence interval=1.14–11.13).

Substance abuse patterns affect the clinical course of PTSD. Overall, the most commonly reported symptoms among persons experiencing an event, whether they met criteria for PTSD or not, were jumpiness (48%), nightmares (43%), and sleep problems (38%). Substance users as a group were no more likely than comparison subjects to report any specific symptoms. However, as shown in table 2, cocaine/opiate users were statistically more likely than comparison subjects to report guardedness, sleep problems, social impairment,

**TABLE 3. Number of PTSD Symptoms and Age at Onset Among Substance Users and Comparison Subjects Exposed to Traumatic Events**

| | | Events | | Symptoms | | Earliest Age at Onset of Posttraumatic Stress Symptoms (years) |
|---|---|---|---|---|---|---|
| Item | N | Mean | SD | Mean | SD | |
| Cocaine/heroin opiates | 62 | 1.37[a] | 0.63 | 3.52[a] | 2.03 | 22[a] |
| Pills/hallucinogens | 36 | 1.24 | 0.49 | 3.14 | 2.03 | 23[a] |
| Marijuana | 55 | 1.11 | 0.37 | 2.25 | 1.48 | 22[a] |
| Heavy alcohol | 61 | 1.25 | 0.60 | 2.36 | 1.67 | 32 |
| Comparison subjects | 215 | 1.16 | 0.55 | 2.57 | 1.86 | 32 |

[a] $p<0.05$, Dunnett's test comparing substance use group with comparison subjects.

**FIGURE 2. Age at First PTSD Symptom by Age at First Drug Use Among 192 Subjects With Both Illicit Drug Use and Any PTSD Symptom**

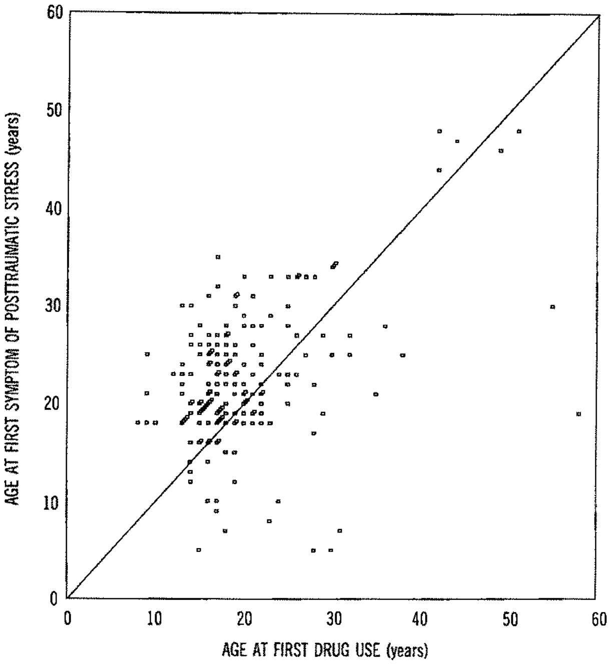
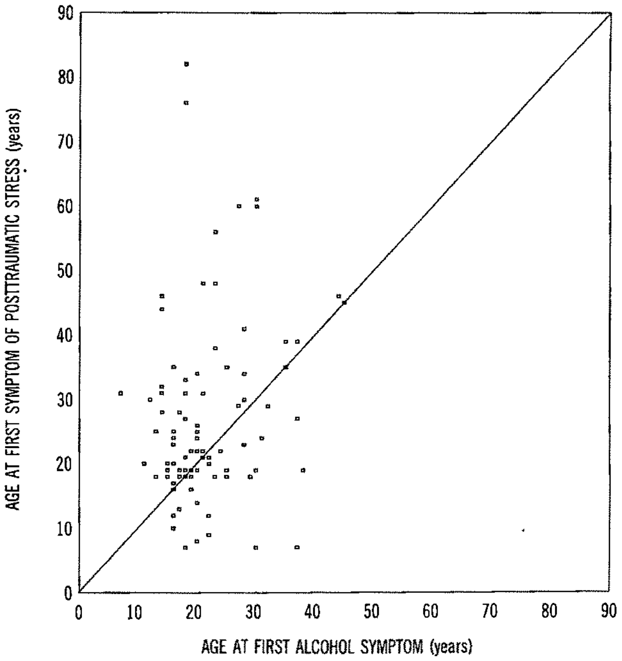


**FIGURE 3. Age at First PTSD Symptom by Age at First Alcohol-Related Symptom Among 192 Subjects With Both Illicit Drug Use and Any PTSD Symptom**



and loss of interest in things they usually cared about. Interestingly, alcoholics were less likely to report situational avoidance than were comparison subjects. After the Bonferroni correction for multiple comparisons was used, only one symptom remained significantly different: cocaine/opiate users were more likely to report social impairment than were comparison subjects.

There was no statistically significant difference between event-exposed substance users and comparison subjects in the mean number of symptoms and events reported, except for cocaine/opiate users. As shown in table 3, they reported more events and symptoms than did comparison subjects. Although users of other classes of drugs did not experience more symptoms or events, they experienced their stressor at a younger age than did comparison subjects.

Age at onset of substance use preceded the onset of event-related symptoms. Several analyses were performed to determine whether the event-related symptoms were experienced before, at the same time as, or after the involvement with substances. First, the age at first symptom from illicit drug use was plotted against the age at first posttraumatic symptom among the 192 persons who reported both illicit drug use and any PTSD symptom (figure 2). The onset of drug use and symptoms related to the stress disorder did not occur at the same time (difference in means is significant at $p<0.0005$), and, in fact, the age at first drug use predated the onset of posttraumatic symptoms. Second, the earliest age at any alcohol-related symptom was then plotted against the age at the first posttraumatic stress symptom (figure 3). Again, alcohol-related problems generally predated the onset of posttraumatic stress symptoms (difference in mean age is significant at $p<0.0001$).

After other variables were controlled, female gender and use of cocaine/opiates predicted PTSD among the subjects exposed to events. Logistic regression was used to investigate the association between certain risk factors and exposure to a PTSD event. Age, race, gender, history of antisocial personality disorder, depression, and substance use pattern were entered into a logistic regression equation model, with exposure to a stressor

**TABLE 4. Logistic Regression Predicting Exposure to Traumatic Events and PTSD**

| | Model Predicting Stressor (N=2,657) | | | Model Predicting PTSD in Subjects Exposed to Events (N=429) | | |
|---|---|---|---|---|---|---|
| Variable | Beta | Standard Error | p | Beta | Standard Error | p |
| Intercept | –1.12 | 0.18 | 0.0001 | –1.43 | 0.72 | 0.05 |
| Age | –0.01 | 0.003 | 0.001 | –0.03 | 0.02 | 0.08 |
| Black | –0.37 | 0.12 | 0.002 | 0.35 | 0.38 | 0.35 |
| Male | –0.44 | 0.13 | 0.0004 | –1.38 | 0.51 | 0.007 |
| Antisocial personality disorder | 0.52 | 0.21 | 0.01 | 0.79 | 0.57 | 0.17 |
| Depression | 0.47 | 0.17 | 0.006 | –0.09 | 0.53 | 0.87 |
| Cocaine/opiates | 1.14 | 0.23 | 0.0001 | 1.19 | 0.57 | 0.04 |
| Pills/hallucinogens | 0.27 | 0.22 | 0.23 | 0.53 | 0.62 | 0.39 |
| Marijuana | 0.19 | 0.18 | 0.30 | –1.57 | 1.06 | 0.14 |
| Heavy alcohol | 0.15 | 0.17 | 0.40 | 0.73 | 0.65 | 0.26 |

as the dependent variable (table 4). Younger age, Caucasian race, female gender, and a history of antisocial personality disorder, depression, and cocaine/opiate use predicted exposure to an event that qualified as a PTSD stressor.

A second logistic regression was performed to predict vulnerability to PTSD among subjects exposed to events. In this evaluation, female gender and use of cocaine/opiates were the only two statistically significant risk factors. When all other variables were controlled, personality, depression, race, and age were not statistically related to PTSD. Of particular interest is the finding (although not statistically significant) that persons exposed to events whose drug use was limited to marijuana were "protected" from the development of PTSD (beta=–1.57).

## DISCUSSION

These data from St. Louis ECA general population subjects support an original hypothesis that illicit substance use increases the risk of exposure to traumatic events and to the subsequent development of PTSD. Specifically, our analyses reveal an increasing relationship between use of more addictive drugs, such as opiates or cocaine, and reports of events that lead to PTSD, as well as vulnerability to PTSD once exposed. Substance users in general were no more likely than comparison subjects to experience a certain type of stressor; however, in contrasting specific types of users with comparison subjects, we found that cocaine/opiate users were more likely than comparison subjects to experience a physical attack. This association is not surprising given the situations in which cocaine/opiate users find themselves (14). However, the low rate of combat-related events among cocaine/opiate users was surprising, since Vietnam-exposed soldiers, individuals assumed to be at high risk for PTSD (1), are also assumed to be at higher risk for heroin use. Alcoholics, on the other hand, were more likely to report combat-related events than were comparison subjects. Data on substance type and event specificity have not previously been provided on this correlation.

A preponderance of PTSD among women in the general population has been previously shown (1). However, our analyses yield a unique finding in that both women and cocaine/opiate users who were exposed to events were found to be significantly more likely to meet criteria for PTSD than were men and persons who did not include cocaine and opiates in their drug use patterns, even after other risk factors, such as age, race, antisocial personality disorder, and depression were controlled. One possible explanation for women's preponderance to develop PTSD may be their greater tendency to report symptoms in general. Cocaine/opiate users may similarly perceive themselves as sicker than nonusers, may interpret their symptoms as more severe, or may be more willing than nonusers to report symptoms and events, which could account for the difference in clinical course (15). Although antisocial personality disorder and depression were not predictive of PTSD, they were associated with exposure to an event even after other factors were controlled. In addition, the fact that younger cohorts were more likely to be exposed to an event may suggest that there is a cohort effect to posttraumatic stress events and that posttraumatic stress is more common than ever before. This certainly has been suggested by a recent general population study by Breslau et al. (16).

The finding that marijuana users were protected from PTSD, but not events, is interesting and deserves further replication. As Penk et al. (17) suggested with their evaluation of MMPI scales for PTSD, this is one of the few disorders affected by personality maturation. If individual variation plays a major role in the development of symptoms, it seems plausible that if persons are able to limit their drug abuse to marijuana, they also could cope better with stress than nonusers. This might explain the low rate of PTSD among subjects who used only marijuana.

We found nightmares, jumpiness, and sleep problems to be the most prevalent symptoms reported, which confirmed the symptom criteria requirements in *DSM-III*. Furthermore, this finding is consistent with data from Ross and colleagues, who suggest that sleep problems are fundamental for PTSD (18).

The analyses showing the onset of drug use and alcohol problems before the onset of PTSD symptoms suggest a possible premorbid vulnerability to PTSD among drug users, a finding that challenges the predicted course suggested by the *DSM-III* manuals of drug abuse complicating PTSD. This potential vulnerability is of considerable importance because it may explain the etiologic link in the association between Vietnam veterans' PTSD and subsequent drug use. Our findings of directionality deserve replication both with different assessment tools and among different populations.

The findings reported here should be interpreted in light of several weaknesses. For example, cross-sectional studies such as the ECA might potentially suffer from recall bias inherent in all studies of retrospective recall. Systematic and standardized questioning, however, minimize this bias to an extent. In addition, the findings are limited by the DIS version used. The ECA study used a methodology for assessing PTSD that was symptom related, rather than event related. However, this should not pose as great a problem as expected because this method would tend to underestimate the rates, rather than overestimate them.

The ECA has provided a unique opportunity to study substance use as a risk factor for both greater exposure to events and subsequent development of PTSD. The strength of our study derives from the fact that it is a general population, non-treatment-seeking sample that included women and nonveterans. Further, the study was not initiated with a PTSD-substance use association in mind. In addition, we feel that the reporting of prevalence rates of PTSD in subjects exposed to traumatic events comes closer to true prevalence rates than any previously reported and should be considered in future analyses on rates of PTSD.

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# Posttraumatic Stress Disorder in an Urban Population of Young Adults: Risk Factors for Chronicity

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*Objective: Despite progress in epidemiologic research on posttraumatic stress disorder (PTSD), little is known about factors that distinguish chronic from nonchronic PTSD. In a previous report, the authors identified a set of personal predispositions associated with PTSD following traumatic events in a general population sample of young adults. The purpose of this analysis was to identify characteristics of chronic PTSD and examine whether any of the suspected risk factors for PTSD was associated specifically with chronic PTSD. Method: A random sample of 1,007 21- to 30-year-old members of a large health maintenance organization in the Detroit area was interviewed, using the National Institute of Mental Health Diagnostic Interview Schedule (DIS), revised for* DSM-III-R. *The analysis was performed on data from 394 respondents who reported traumatic events, of whom 93 met criteria for PTSD. Chronic PTSD was defined as duration of symptoms for 1 year or more. Results: Persons with chronic PTSD (N=53) had, on the average, a significantly higher total number of PTSD symptoms and higher rates of overreactivity to stimuli that symbolized the stressor and interpersonal numbing than persons with nonchronic PTSD. The rates of one or more additional anxiety or affective disorders and a variety of medical conditions were higher in persons with chronic than nonchronic PTSD. Family history of antisocial behavior and female sex were associated specifically with chronic PTSD. Conclusions: The findings suggest that chronic PTSD may be associated with specific risk factors and clinical features. Longitudinal data on the course of PTSD are needed to determine whether the distinct features and the medical and psychiatric histories of persons with chronic PTSD are complications attendant on a chronic course or coexisting disturbances that inhibit recovery.*

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Epidemiologic studies have confirmed previous reports of persistent psychiatric morbidity in Vietnam combat veterans and have provided evidence that an important determinant of chronic posttraumatic stress disorder (PTSD) is level of combat exposure (1–5). A similar observation with respect to level of exposure was made in regard to chronic PTSD among survivors of a civilian disaster (6, 7). The definition of PTSD in *DSM-III-R* requires that the disturbance lasts for at least 1 month. However, unlike *DSM-III*, *DSM-III-R* does not specify subtypes of PTSD, classified according to duration of symptoms. Nonetheless, chronicity in PTSD continues to be an important clinical and research issue (8, 9). While there is evidence that a high level of exposure to combat and to civilian disasters may be associated with chronic PTSD, little is known about how chronic PTSD differs from nonchronic PTSD and why PTSD symptoms subside in some affected persons but persist for long periods in others.

Previously, we reported on the lifetime prevalence of PTSD and potential risk factors associated with its occurrence in a random sample of young adults selected from the membership of a large health maintenance organization (HMO) in the Detroit area (10). Of 1,007 respondents, 394 reported that they had experienced in their lifetime typical PTSD stressors and 93 met *DSM-III-R* criteria for PTSD. With the exception of rape, differences in the rate of PTSD across classes of traumatic events were relatively small. The following six factors were found to be associated with greater vulnerability to PTSD following exposure to traumatic events: female sex, prolonged childhood separation from parents, family history of anxiety, family history of antisocial behavior, preexisting anxiety or depression, and neuroticism. These results applied to the entire subset with PTSD regardless of the duration of symptoms beyond the 1-month diagnostic requirement.

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**TABLE 1. Lifetime Prevalence of PTSD, by Various Duration Criteria, in Urban Young Adults**

| | Lifetime Prevalence of PTSD | | | | | |
|---|---|---|---|---|---|---|
| | Total (N=1,007) | | Men (N=386) | | Women (N=621) | |
| Duration Criterion | N | % | N | % | N | % |
| 1 month or longer | 93 | 9.2 | 23 | 6.0 | 70 | 11.3 |
| 6 months or longer | 71 | 7.1 | 18 | 4.7 | 53 | 8.5 |
| 1 year or longer | 53 | 5.3 | 9 | 2.3 | 44 | 7.1 |
| 3 years or longer | 34 | 3.4 | 5 | 1.3 | 29 | 4.7 |

In the present study we focused on chronic PTSD, defined as duration of symptoms for 1 year or longer. We examined the characteristics of chronic PTSD and inquired whether any of the personal dispositions, identified as predictors of who developed PTSD following exposure, was associated specifically with chronic PTSD. Because persistent psychiatric disturbances are associated with disabilities and greater use of health care, an analysis of factors associated with chronicity of PTSD is of great clinical importance.

## METHOD

A detailed description of the sample and the measurement instruments was provided previously (10). Briefly, a random sample of 1,200 was selected from all 21- to 30-year-old members of a 400,000-member HMO in the Detroit metropolitan area. A total of 1,007 (84%) were interviewed at their homes in 1989; 81% were white and 19% were black; 62% of the sample were women. The National Institute of Mental Health Diagnostic Interview Schedule (DIS), revised to cover *DSM-III-R* disorders, was used. The revised DIS section on PTSD opens with a question in which several typical PTSD events are mentioned, and respondents were asked whether any of these events had ever happened to them. A report of an event that did not fit the *DSM-III-R* stressor definition (e.g., illness, death in the family, divorce) was excluded from further inquiry, and the respondent was asked whether or not he or she had experienced another event of the sort described in the question. A respondent's report of a PTSD-type stressor was followed by questions about the occurrence of PTSD symptoms after the event. Information was gathered on age at exposure, the time of onset of symptoms, and their duration. In addition, the interview covered psychiatric disorders in parents and siblings, a history of prolonged childhood separation from parents, personality factors, and sociodemographic characteristics.

Chronic PTSD was defined as duration of symptoms for at least 1 year. While the concept of chronicity is widely used in clinical psychiatry, the choice of a precise quantitative definition is in part an arbitrary decision. Chronic PTSD, as a subtype, was deleted from *DSM-III-R,* probably because of lack of evidence supporting any single cutoff point. This is not unique to PTSD; there are no definitions of chronic subtypes of any psychiatric disorder in *DSM-III-R.* With respect to axis I disorders in which nontransient, or prolonged, disturbance is a defining feature (rather than a characteristic of a subtype), duration criteria vary from 6 months (generalized anxiety disorder) to 2 years (dysthymia or cyclothymia). While we could have chosen 6 months as a cutoff, following the previous rule in *DSM-III,* our purpose was to define a threshold for chronic PTSD, rather than to separate acute (or transient) from nonacute (or nontransient) reactions. There are also precedents in the research literature supporting the 1-year cutoff for chronic PTSD (11). Furthermore, in our sample of young adults, 1 year was the median of the duration distribution.

Of the 93 respondents who met criteria for PTSD, 70 were in remission during the year before the interview. Duration of PTSD was estimated for these subjects by subtracting the age at onset from the age at which the last symptom was experienced. Duration of PTSD could not be estimated for 23 persons who continued to experience symptoms during the year before the interview. However, with one exception, all persons with active cases of PTSD reported that their PTSD symptoms had appeared more than 1 year earlier and were thus classified as having chronic PTSD. The single person with an active case with symptoms lasting less than 1 year was not included in the analysis.

The strength of the association of chronic PTSD with suspected risk factors was measured by the odds ratio, calculated in tables of cross-tabulations, by using exposed persons with no PTSD as a reference. A multivariable logistic regression was used to estimate the odds ratio of each factor, adjusted for all other factors in the model. Goodness-of-fit chi-square was used to estimate the efficacy of the model (12). The sensitivity and specificity of the model for predicting chronic PTSD were calculated by using cutoff points that minimize the weighted misclassification rate.

## RESULTS

### *Lifetime Prevalence of PTSD and Chronic PTSD*

Of the 1,007 respondents, 394 had been exposed to traumatic events and 93 (9.2%) met *DSM-III-R* criteria for PTSD. More than three-quarters of those who met PTSD criteria reported symptoms lasting 6 months or more. However, in 43%, PTSD symptoms had resolved in less than 1 year, leaving 57% with symptoms that persisted for 1 year or more (table 1). Women were at greater risk for PTSD than men, even though they were not more likely than men to be exposed to traumatic events (10). Moreover, while they constituted 65% of those with PTSD of less than 1 year's duration, women constituted 83% of those with PTSD symptoms lasting 1 year or more.

The approximately 50% split between chronic and nonchronic PTSD, with the 1-year cutoff as a criterion, ap-

TABLE 2. Prevalence of Individual PTSD Symptoms in Urban Young Adults With Chronic and Nonchronic PTSD

| | Prevalence (%) | | | |
|---|---|---|---|---|
| Symptom | Chronic PTSD (N=53) | Nonchronic PTSD (N=40) | $\chi^2$ (df=1) | p |
| Recurrent recollections | 94.3 | 95.0 | 0.02 | 0.89 |
| Recurrent dreams | 79.2 | 80.0 | 0.008 | 0.93 |
| Flashbacks | 49.1 | 50.0 | 0.008 | 0.93 |
| Avoid thoughts | 86.8 | 90.0 | 0.23 | 0.64 |
| Avoid activities | 84.9 | 82.5 | 0.10 | 0.76 |
| Psychogenic amnesia | 24.5 | 27.5 | 0.11 | 0.75 |
| Psychologic reactivity to symbolic stimuli | 67.9 | 45.0 | 4.92 | 0.03 |
| Physiologic reactivity to symbolic stimuli | 64.2 | 40.0 | 5.35 | 0.02 |
| Diminished interest | 62.3 | 55.0 | 0.50 | 0.48 |
| Foreshortened future | 32.1 | 25.0 | 0.55 | 0.46 |
| Detachment from others | 90.6 | 67.5 | 7.77 | 0.005 |
| No loving or warm feelings | 62.3 | 37.5 | 5.60 | 0.02 |
| Sleep problems | 84.9 | 70.0 | 3.00 | 0.08 |
| Irritability/anger | 60.4 | 57.5 | 0.08 | 0.78 |
| Problem concentrating | 88.7 | 70.0 | 5.10 | 0.02 |
| Hypervigilance | 83.0 | 95.0 | 3.14 | 0.08 |
| Startle | 69.8 | 55.0 | 2.16 | 0.14 |

plied to nearly all types of events, including rape, a traumatic event associated in this study with an exceptionally high rate of PTSD (10). Personally experienced violence, that is, sudden injury or accident, physical assault, and rape, was not more likely to lead to chronic symptoms than were vicarious experiences, such as seeing someone seriously hurt or killed or receiving news of the violent death of or injury to a close relative or friend.

### *Symptoms of Chronic and Nonchronic PTSD*

Table 2 displays the prevalence of *DSM-III-R* criteria symptoms of PTSD in the chronic and nonchronic subsets. Because this analysis was exploratory in purpose, we did not adjust the alpha level for the greater chance of type I error because of multiple interrelated tests. A caveat regarding the interpretation of these results is in order.

Reexperiencing the trauma in intrusive thoughts, nightmares, or flashbacks was equally common in the chronic and nonchronic subsets. Similarly, symptoms of avoidance, diminished interest in previously salient activities, and foreshortened future were experienced in equal rates by persons with chronic and nonchronic PTSD. However, in two symptom domains, chronic PTSD was associated with higher rates of symptoms: overreactivity (both psychologic and physiologic) to stimuli that symbolized the traumatic event and interpersonal numbing, as manifested by detachment from others and diminished positive affect. Concentration problems were also significantly more common in persons with chronic than nonchronic PTSD. The mean number of PTSD symptoms in chronic and nonchronic PTSD was 12.8 (SD=2.6) and 11.4 (SD=2.6) (t=2.54, df=90, p=0.01).

TABLE 3. Prevalence and Sex-Adjusted Odds of Other *DSM-III-R* Disorders in Urban Young Adults With Chronic and Nonchronic PTSD

| | Prevalence (%) | | | |
|---|---|---|---|---|
| *DSM-III-R* Disorder | Chronic PTSD (N=53) | Nonchronic PTSD (N=40) | Adjusted Odds Ratio | 95% Confidence Interval |
| Any affective or anxiety disorder | 81.1 | 57.5 | 2.86 | 1.10–7.39 |
| Major depression | 39.6 | 32.5 | 1.24 | 0.50–2.99 |
| Dysthymia | 9.4 | 0.0 | | |
| Mania | 9.4 | 0.0 | | |
| Any anxiety disorder[a] | 66.0 | 47.5 | 1.87 | 0.78–4.45 |
| Alcohol abuse or dependence | 35.8 | 25.0 | 2.70 | 0.94–7.78 |
| Drug abuse or dependence | 18.9 | 25.0 | 0.78 | 0.28–2.17 |

[a] Includes panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, and phobia.

### *Co-Occurrence of Other Psychiatric Disorders and Medical Conditions*

In table 3 appear the lifetime rates of affective and anxiety disorders and alcohol and illicit drug abuse or dependence in persons with chronic and nonchronic PTSD. Because the rates of these disorders vary by sex, and because chronicity of PTSD was observed to be sex-related, sex-adjusted odds ratios were used to estimate the associations of these disorders with chronic, compared to nonchronic, PTSD. With one exception, the rates of the disorders listed in table 3 were higher in persons with chronic than nonchronic PTSD. Illicit drug abuse or dependence was more common in the nonchronic group. The highest odds ratio was associated with any affective or anxiety disorder (odds ratio=2.86, 95% confidence interval=1.10–7.39). Manic episodes and dysthymia were reported only by persons with chronic PTSD, with 9.4% of the subset reporting each.

Persons with chronic and nonchronic PTSD were compared on self-reported lifetime histories of 11 medical conditions. On the average, persons with chronic PTSD had more self-reported medical conditions than persons with nonchronic PTSD, 1.9 (SD=1.6) versus 1.0 (SD=0.8), respectively (t=3.46, df=90, p<0.001). Because one condition—gynecologic complaints—applied only to women, we compared the two groups on number of medical conditions, deleting gynecologic complaints. The means were 1.5 (SD=1.5) versus 0.8 (SD=0.8), respectively (t=2.63, df=90, p=0.01). Each of the following conditions was significantly more common in the chronic than the nonchronic subset: arthritis (26% [N=14] versus 10% [N=4]), bronchitis (21% [N=11] versus 0%) migraine (43% [N=23] versus 2% [N=1]), and gynecologic complaints among women (55% [N=24] versus 31% [N=8]).

### *Risk Factors for Chronic PTSD*

We present, in table 4, the rates of chronic PTSD according to the presence or absence of five of the six

**TABLE 4. Risk Factors for Chronic (1 Year or More) PTSD in Urban Young Adults Exposed to Traumatic Events (N=354)**

| | Prevalence of Chronic PTSD (%) | | | |
|---|---|---|---|---|
| Risk Factor | Persons With Risk Factor | Persons Without Risk Factor | Odds Ratio | 95% Confidence Interval |
| Female sex | 21.8 | 5.9 | 4.43 | 2.09–9.39 |
| Early separation | 35.7 | 13.2 | 3.66 | 1.58–8.44 |
| Family history of anxiety | 26.7 | 8.1 | 4.15 | 2.24–7.70 |
| Family history of antisocial behavior | 34.7 | 10.0 | 4.79 | 2.57–8.92 |
| Preexisting anxiety or affective disorder | 34.6 | 13.4 | 3.42 | 1.43–8.14 |

suspected risk factors identified in our previous report (10). (Persons with nonchronic PTSD were deleted from these calculations.) Women were more than fourfold more likely than men to develop chronic PTSD after exposure to traumatic events. Separation from parents in childhood, family history of anxiety, and family history of antisocial behavior increased the odds for chronic PTSD, each by approximately fourfold. A history of preexisting anxiety or affective disorder at time of exposure to traumatic events was associated with a threefold increase in the likelihood of chronic PTSD. In addition, persons with chronic PTSD had, on the average, markedly higher scores on the Eysenck's Neuroticism Scale (mean=7.0, SD=2.9) than persons with no PTSD (mean=4.2, SD=3.1) (t=6.20, df=352, p<0.0001).

A multivariable logistic regression analysis was used to estimate the odds for chronic PTSD associated with each of the factors when all other factors were controlled. The results, which appear in table 5, show that each of the individual factors, independently of the others, increased significantly the risk for chronic PTSD (goodness-of-fit $\chi^2$ [Hosmer-Lemeshow]=8.41, df=8, p=0.39). The sensitivity of the model for predicting chronic PTSD was 75.5 and its specificity, 71.4%.

To evaluate whether these findings were specific to chronic PTSD, an analogous analysis was performed for nonchronic PTSD. The results (not shown) indicated that four of the factors found to increase the risk for chronic PTSD were implicated also in nonchronic PTSD: early separation from parents, family history of anxiety, preexisting anxiety or depression, and neuroticism. In contrast, family history of antisocial behavior, an important factor in chronic PTSD, was unrelated to nonchronic PTSD. In addition, women were not significantly overrepresented among persons with nonchronic PTSD. A multivariable logistic regression (not shown) revealed that only two factors, early separation from parents and family history of anxiety, were associated with significant increases in the risk for nonchronic PTSD when all other risk factors were controlled. The utility of the model for predicting nonchronic PTSD fell far below that for chronic PTSD, judging from a comparison of its sensitivity and specificity estimates to corresponding estimates for the model of chronic PTSD (goodness-of-fit $\chi^2$=13.22, df=8, p=0.11). The sensitivity of the model for predicting nonchronic PTSD was 55% and the specificity, 68.8%.

**TABLE 5. Multivariable Logistic Regression of Suspected Risk Factors for Chronic PTSD in Urban Young Adults**

| Risk Factor | Adjusted Odds Ratio | 95% Confidence Interval |
|---|---|---|
| Female sex | 2.83 | 1.23–6.49 |
| Early separation | 4.11 | 1.46–11.54 |
| Family history of anxiety | 3.28 | 1.60–6.69 |
| Family history of antisocial behavior | 3.49 | 1.70–7.15 |
| Preexisting anxiety or depression | 3.27 | 1.18–9.12 |
| Neuroticism[a] | 1.86 | 1.30–2.67 |

[a] Odds of chronic PTSD associated with an increase of one standard deviation.

## DISCUSSION

The findings of this study can be summarized as follows. 1) Of all 93 persons with PTSD in this sample of young adults, approximately one-half continued to experience symptoms for 1 year or longer. 2) When the subset with symptoms of 1 year's duration or longer was defined as having chronic PTSD, a similar reduction in the rate of chronic PTSD from the total rate of PTSD of 1 month's duration was observed across most types of events. 3) Compared to those with nonchronic PTSD, persons with chronic PTSD were more likely to experience psychologic and physiologic overreactivity to stimuli symbolic of the traumatic events, as well as interpersonal numbing. 4) Compared to nonchronic PTSD, chronic PTSD was associated with greater prevalence of any anxiety or affective disorder and a variety of medical conditions. 5) Four factors—early separation from parents, family history of anxiety, preexisting anxiety or depression, and neuroticism—were associated with greater odds for PTSD of either duration category. 6) Two factors were associated specifically with chronic PTSD: family history of antisocial behavior and female sex. 7) The set of suspected risk factors had a substantially greater utility in predicting chronic than nonchronic PTSD.

The interpretation of the results concerning suspected risk factors must take into account the cross-sectional design of the study. Prospective studies in which risk factors are measured before the onset of disease are needed to guard against the potentially biasing effects of a history of psychiatric disorder on respondents' reports about risk factors.

The lifetime prevalence of chronic PTSD among those who were exposed to typical PTSD events in this study was 13.4% (N=53 of 394), a figure close to the recent estimate of 15% of Vietnam combat veterans with chronic PTSD (1). Our definition of chronicity specified a duration that was markedly less than the 15–20-year period that had separated the Vietnam war from the time of the veterans' assessment. Although we found no evidence in this study that the nature of stressors was the primary determinant of the persistence of PTSD symptoms, the array of traumatic events experienced by the respondents in this study did not include combat or other war-related events. On two counts, combat experience can be viewed as distinctive (13). First, it consists of multiple events spread over a prolonged period. Second, the moral complexity of combat experience differs from other types of traumatic events, in that those who are exposed are simultaneously the victims, perpetrators, and witnesses of violence. These unique characteristics may be particularly relevant to the persistence of PTSD symptoms among Vietnam combat veterans.

We found that chronic PTSD was characterized by more PTSD symptoms than nonchronic PTSD, a finding consistent with the general tendency for chronicity of disorder to be associated with more pervasive or severe symptoms. The identification of disturbances associated specifically with chronic PTSD—overreactivity to stimuli that represent the trauma and interpersonal detachment—may offer some insight into the persistence of PTSD. The first disturbance represents the generalization of the arousal response beyond the concrete event, a psychologic process that can lead to self-imposed restrictions or avoidance of activities and may hinder recovery. The clinical significance of the second disturbance, that is, interpersonal numbing, stems from its association with social isolation, a factor that has long been viewed as a determinant of psychiatric disorders, especially depression (14–16).

Persons with chronic PTSD were more likely than those with nonchronic PTSD to experience in their lifetime at least one other anxiety or affective disorder. Additional analysis confirmed that the greater odds for any anxiety or affective disorder in persons with chronic versus nonchronic PTSD were independent of the effects of sex and family history of antisocial behavior, factors associated with greater risk for chronic PTSD. The higher lifetime rates of psychiatric disorders other than PTSD in persons with chronic PTSD might signal greater predisposition to psychopathologic reactions to traumatic events, a greater risk for the development of secondary disorders, or the contribution of concurrent disorders to the maintenance of PTSD symptoms.

Of the six suspected risk factors for PTSD identified in our previous report (10), four were found to be associated with nonchronic PTSD: early separation from parents, family history of anxiety, preexisting anxiety or depression, and neuroticism. Nonchronic PTSD was unrelated to family history of antisocial behavior and female sex. In contrast, chronic PTSD was associated with the entire set of factors. Thus, our findings suggest that certain personal dispositions increase the likelihood of PTSD following traumatic events, while a subset of these factors increases the risk for chronicity of PTSD symptoms. It should be noted that the two factors associated specifically with chronic PTSD, family history of antisocial behavior and female sex, have been previously linked, in an essential way, to somatization disorder and related diagnoses (17–19), a class of disorders in which chronicity is a hallmark.

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# Symptom Responses of Female Vietnam Veterans to Operation Desert Storm

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*Objective: This study examined the status of symptoms of posttraumatic stress disorder (PTSD) in a cohort of women after the onset of Operation Desert Storm. Method: Seventy-six non-treatment-seeking Vietnam veterans were obtained from lists of those who recently had participated in other research projects conducted at the National Center for Post-Traumatic Stress Disorder. Before the onset of Operation Desert Storm, subjects had completed a set of psychometrically valid instruments measuring general psychological symptoms and PTSD symptoms (e.g., SCL-90-R, Mississippi Scale for Combat-Related Posttraumatic Stress Disorder). On the basis of the latter scale, subjects were divided into groups with and without PTSD symptoms. At the height of the military conflict, subjects were recontacted and asked to complete the SCL-90-R and the Veterans Update Form, a measure assessing changes in PTSD symptoms. Results: Multivariate analyses indicated that while most female Vietnam veterans experienced some intensification of stress-related symptoms during Operation Desert Storm, those who had previously reported high levels of PTSD were significantly more susceptible to greater distress. Conclusions: Results of this survey indicate that female Vietnam veterans with prior wartime exposure are an at-risk population for the intensification of stress symptoms after the recurrence of a military conflict.*

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Events that resemble prior traumatizing experiences can reactivate symptoms of posttraumatic stress disorder (PTSD) (1–3). For example, some combat veterans have shown a reemergence or exacerbation of previous stress reactions when they are reexposed to combat in the course of additional military service (4). Similarly, Israeli children who have lost parents in terrorist attacks have evidenced the reemergence or exacerbation of PTSD symptoms when reexposed to war or further terrorist activities (5). In all of these instances, direct reexposure to events similar to the original precipitant resulted in significantly increased symptoms.

Other data suggest that indirect exposure or exposure to more abstract cues, for example, those symbolizing aspects of the original event, can provoke reactions in some individuals. For example, case studies of three male Vietnam veterans following their attendance at a dedication ceremony for the Vietnam Memorial showed that all three experienced increased PTSD symptoms (6). In a subsequent study of 94 male Vietnam veterans, Parsons et al. found that both those who attended and those who did not attend the Vietnam Memorial's dedication showed intensification of stress symptoms, especially anxiety, guilt, and sleep disturbance (7). The authors hypothesized that a range of factors including media accounts and community reactions to the dedication contributed to the veterans' increased sensitivity. Thus, a variety of cues related to the original event can be influential in exacerbating or retriggering symptoms.

The recent activities of Operation Desert Storm have received extensive, detailed media coverage and have generated considerable public concern. Recent anecdotal reports by clinicians have suggested that the onset of this war may have reactivated or intensified stress symptoms in some percentage of American war veterans (8). To date, there are no empirical data to substantiate this impression. The present study surveyed female Vietnam veterans by mail to examine whether PTSD symptoms recurred or intensified in a 2-week period after the start of Operation Desert Storm on Jan. 16, 1991. Participants were also surveyed on a range of

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other psychological symptoms and on their use of mental health treatment services to gain additional information about the war's impact.

## METHOD

### *Subjects*

Subjects in this study included 76 female Vietnam veterans. (A cohort of 49 female World War II veterans served as a comparison group. Data on this cohort are available from Dr. Wolfe.) Their average age was 49.6 years (range=37–72). Average war-zone exposure for this group would be described as moderate on the basis of previously obtained information (J. Wolfe, J. Furey, P.J. Brown, et al., Women's War-time Exposure Scale, 1990, unpublished manuscript). "Moderate" in this context reflects intermittent exposure to dangerous or life-threatening events (e.g., incoming rocket or mortar attacks), close contact with the dead and dying, and other similar severe stressors.

All women volunteered to participate in this project without reimbursement. Participants did receive a follow-up letter thanking them for their assistance and a summary of the survey's results.

### *Procedure*

The participants were drawn from lists previously compiled by one of us (J.W.) for use in projects at the National Center for Post-Traumatic Stress Disorder, Women Veterans Program. Because female veterans are often difficult to locate, many names were assembled through the assistance of other veterans. Pre-Operation Desert Storm psychometric data—scores on the SCL-90-R (9) and a revised version of the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (10)—were available for those women who had previously participated in another research project at the national center. No participants were seeking services for PTSD from the Women Veterans Program at the time of the survey.

Participants were contacted by mail in late February–early March 1991 and were asked to complete the Veterans Update Form (J. Wolfe, 1991, unpublished manuscript) and the SCL-90-R (9). The SCL-90-R, rather than a PTSD instrument, was selected to provide more general indices of psychological distress. Subjects who did not reply were not contacted again by mail because of the limited period for inquiry.

The project had an overall return rate of 29%. The rate of return was partially affected by mailing constraints; approximately 7% of the surveys lacked correct current addresses. Telephone contact with 10% of the nonrespondents who were comparable in age, education, and war-zone exposure to respondents indicated no difference on any items of the survey questionnaire between these two groups. Furthermore, analyses of pre-Operation Desert Storm data on the SCL-90-R revealed no significant differences between nonrespondents and subjects who participated in the study.

### *Psychometric Assessment*

*Veterans Update Form.* A brief self-report measure was developed for the study to delineate change in the three *DSM-III-R* cardinal PTSD symptoms of reexperiencing, avoidance/numbing, and hyperarousal after the onset of Persian Gulf warfare involving American troops. Questions were based on a 5-point Likert-type scale; scores ranged from 0 (no change) to 4 (extremely increased) for each major symptom category. Respondents also answered several questions about their past and current use of psychological treatment as well as changes in mental health needs, with Jan. 16, 1991, used as the point of reference.

*SCL-90-R.* This widely used, 90-item, self-report measure instructs subjects to rate a series of broad-based psychological symptoms. Traditional symptom ratings of 0 (no distress) to 4 (very distressed) were employed. Scoring yields nine scaled symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Empirical research on this instrument has documented satisfactory reliability and validity for each of the symptom scales (9).

*Revised Mississippi Scale for Combat-Related Posttraumatic Stress Disorder.* Participants had previously completed the revised Mississippi scale, a variation of the 35-item, self-report scale designed to measure the cardinal symptoms of PTSD. Prior research has demonstrated that the scale possesses acceptable reliability and validity as well as other psychometric properties (sensitivity=0.93, specificity=0.89, overall efficiency=0.90) (10). The revised version incorporated minor semantic changes in three questions that previous pilot data indicated were inappropriately phrased for use with female veterans.

### *Statistical Analyses*

On the basis of previously available data, the Vietnam cohort was divided into groups with and without PTSD. A series of analyses of variance (ANOVAs) was used to compare group symptom reports by using current *DSM-III-R* criteria for PTSD. Chi-square analyses were carried out to assess any treatment utilization differences. Multivariate analyses of variance (MANOVAs) and analyses of covariance (ANCOVAs) were then conducted to examine changes in SCL-90-R profiles for the two Vietnam veteran groups.

## RESULTS

Previously collected data on PTSD symptoms (scores on the Mississippi scale for PTSD) before Operation Desert Storm were used to divide the Vietnam cohort

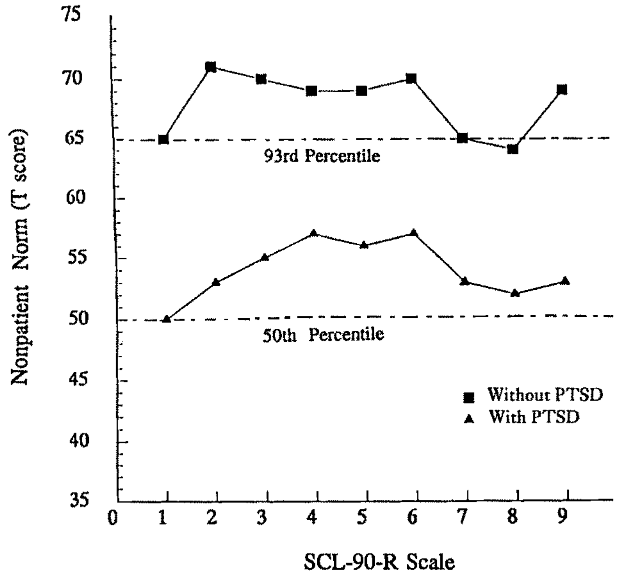
**TABLE 1. PTSD Symptom Change After the Beginning of Operation Desert Storm for Female Vietnam Veterans Without and With PTSD[a]**

| | Without PTSD[b] (N=50) | | With PTSD (N=26) | | ANOVA | | |
|---|---|---|---|---|---|---|---|
| Symptom | Mean | SD | Mean | SD | F | df | p |
| Reexperiencing | 1.2 | 1.3 | 2.4 | 1.3 | 14.35 | 1, 74 | <0.001 |
| Avoidance/numbing | 0.7 | 1.2 | 2.3 | 1.2 | 29.58 | 1, 74 | <0.0001 |
| Hyperarousal | 1.2 | 1.4 | 2.7 | 1.0 | 23.49 | 1, 74 | <0.0001 |

[a] 0=no change, 1=slightly increased, 2=somewhat increased, 3=very increased, 4=extremely increased.

[b] The t tests comparing symptom changes in this group from before to after Operation Desert Storm indicated greatest increases for symptoms of reexperiencing (t=3.34, df=49, p<0.005) and hyperarousal (t=3.27, df=49, p<0.005).

**FIGURE 1. Mean SCL-90-R Scores During Operation Desert Storm for Female Vietnam Veterans Grouped by Scores on the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder**



into groups without PTSD (N=50) and with PTSD (N=26) groups. These groupings are comparable to divisions used with male Vietnam combatants to determine the PTSD diagnosis (10). Mean *DSM-III-R* PTSD symptom scores were then calculated for both Vietnam groups (table 1). One-way ANOVAs indicated that the group with PTSD had significantly greater increases than the group without PTSD across all three current PTSD ratings: reexperiencing, avoidance/numbing, and hyperarousal. In the group without PTSD, increases were greatest for symptoms of reexperiencing and hyperarousal. There were no such differences for the group with PTSD.

A MANOVA was conducted on the SCL-90-R protocols completed by women in the two groups after the start of Operation Desert Storm; univariate tests showed significant differences between the two groups on all nine dimensions (p<0.005). A series of ANCOVAs was subsequently carried out on the post-Operation Desert Storm SCL-90-R protocols, with pre-Operation Desert Storm SCL-90-R data as covariates. The group with PTSD had significantly higher levels than the group without PTSD on the following three dimensions: somatization (F=11.11, df=1, 71, p<0.005), obsessive-compulsive (F=17.59, df=1, 71, p<0.001), and hostility (F=7.55, df=1, 71, p<0.01). As can be seen in figure 1, the group with PTSD had postwar SCL-90-R T scores that averaged around the 93rd percentile.

With respect to mental health treatment status before and after the start of the war, more veterans with PTSD than veterans without PTSD reported receiving treatment at some point before Operation Desert Storm ($\chi^2$=12.80, df=1, p<0.0005.). Of those veterans not currently in treatment, more with PTSD than without it thought that they should be receiving treatment for PTSD ($\chi^2$=6.61, df=2, p<0.05).

## DISCUSSION

These results offer some of the first empirical data on veterans' responses to the recent crisis in the Middle East. Female Vietnam veterans clearly have been affected to some degree by the recent initiation of a large-scale U.S. military conflict. Because the survey was conducted close to the conclusion of the war, when a cease-fire was imminent, it is likely that these findings represent a conservative estimate of the war's impact on veterans.

Analyses of responses indicated that female Vietnam veterans with high levels of preexisting PTSD symptoms showed greater increases across symptom dimensions, which suggests that they were most vulnerable to symptom exacerbation after reexposure. This finding is consistent with reports that individuals who are unable to resolve or integrate earlier traumatic experience are at significant risk for the retriggering of stress-related symptoms when they are faced with events similar to the original stressor (11). Nonetheless, the demonstrated symptom increase across the Vietnam cohort in general suggests that a variety of veterans were at risk for reemergence of symptoms after the start of Operation Desert Storm. This broader pattern of reactivity is consonant with clinical reports from various sites within the Veterans Affairs system which indicate that two types of male veterans have recently sought increased treatment: those previously known to have problems with PTSD and those who were apparently asymptomatic before the start of the Gulf conflict (8).

The issue of more indirect forms of stressor exposure, as raised in this study, is important. As with other types of traumatic events (e.g., rape), a wide range of environmental cues appear capable of stimulating symptomatic response in previously exposed individuals. The majority of the Vietnam cohort in this study were theater veterans, many of whom felt that they knew firsthand what military personnel were undergoing in the war zone.

In the case of Operation Desert Storm, an unusually large array of cognitive and perceptual cues is likely to have added to the reactions felt among both those who had and those who had not been exposed to a war zone. Media coverage was extensive, and public and community response, while generally positive, served to heighten awareness of the war's presence and its potentially dangerous consequences. Anticipation of loss or trauma may also have played a role in veterans' reactions to the events of war. In a recent study conducted before the onset of Operation Desert Storm, anticipatory anxiety was found to contribute to a range of symptomatic responses in military wives and children of troops deployed to the Persian Gulf (12). Thus, a variety of factors influence coping and adjustment under stress.

One particular strength of this study is that it contained symptom measures obtained before the start of Operation Desert Storm, which permitted controlled comparison of changes in response to the war. Results suggested increases in levels of general psychiatric distress (e.g., somatization, hostility) that may extend beyond the specific diagnostic criteria for PTSD. Inspection of items on the obsessive-compulsive scale (elevated in the group with PTSD) indicated that many of the endorsed items reflect symptoms consonant with intensification of stress syndromes, for example, increased ruminative or intrusive thoughts. Further examination of the SCL-90-R scales in conjunction with broader diagnostic assessments will help to delineate the nature of symptom intensification after reexposure and its specificity for the PTSD diagnosis.

At the present time, there are no data on whether veterans who experienced increased symptoms secondary to the onset of Operation Desert Storm are at greater risk for subsequent psychological or health-related problems; consequently, planning of treatment resources remains uninformed. Data from this study suggest that it is important for mental health professionals to attend to factors associated with the reemergence of stress reactions and to consider the need for early clinical intervention. The importance of such intervention is supported by Laufer and others who have observed the adverse effects of recurrent war stress on subsequent functioning throughout the life span (13).

Overall, the data in this study suggest that further investigation of the response of previously exposed veterans to subsequent trauma is also worthwhile for scientific purposes. Tracking of these responses is required to determine whether these reactions are sustained and, if so, what their effect is on social and vocational functioning. In addition, future research comparing female veterans' responses to those of male veterans will shed light on whether gender is a factor in the genesis and mediation of the response to recurrent life trauma (14).

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# Suicidal Ideation and Suicide Attempts Among Patients With Panic Disorder: A Survey of Two Outpatient Clinics

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*Objective: Recent epidemiologic studies found that 20% of subjects with the diagnosis of panic disorder had attempted suicide. This study sought to determine the prevalence of suicidal ideation and suicide attempts among patients with panic disorder and whether the presence of comorbid borderline personality disorder influenced the prevalence of suicidal thoughts and behavior. Method: At two outpatient clinics, experienced clinicians conducted retrospective reviews of data from the intake interviews and charts of 59 patients with panic disorder and comorbid borderline personality disorder and 234 patients with panic disorder with or without axis II disorders other than borderline personality disorder. Results: Suicide attempts were reported by 2% of the patients with panic disorder, compared to 25% of the patients with both panic disorder and borderline personality disorder. In addition, 2% of the patients with panic disorder, compared to 27% of the patients with panic disorder and borderline personality disorder, reported suicidal ideation that was judged to be of clinical significance. Conclusions: The rate of suicidal ideation and suicide attempts for psychiatric outpatients with panic disorder was discrepant with the findings of the earlier studies. The increased suicide risk in this group of patients was associated with borderline personality disorder, increased substance abuse, and affective instability. While 61% of the panic disorder patients and 78% of the patients with both panic disorder and borderline personality disorder reported thinking about death, this must be distinguished from actual suicidal ideation and clinical risk of suicide.*

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A reanalysis of data from the Epidemiologic Catchment Area (ECA) study on the prevalence of suicidal ideation and suicide attempts among persons with psychiatric disorders was recently conducted by Weissman et al. (1). They found that 20% of patients with panic disorder had made a suicide attempt. These findings are surprising, since individuals with major affective disorders, schizophrenia, and some personality disorders have been considered to be at greater risk for suicidal behavior than those with panic disorder. The findings could also be quite disconcerting to clinicians who treat patients with panic disorder. Weissman and colleagues (1, 2) concluded 1) that suicide attempts were associated with panic disorder in both its complicated and uncomplicated forms and 2) that the risks were comparable to that associated with major depression. Since these findings have far-reaching implications, further study of the prevalence of suicidal ideation and suicide attempts among patients with panic disorder is warranted.

Careful examination of the two reports by Weissman and associates (1, 2) revealed two issues that might benefit from further exploration. First, for questions addressing suicidal ideation, the clinical severity and precise nature of the ideation were not reported. Second, data on the timing of the suicide attempts were not available, and thus the attempts may not have been concurrent with or related to the disorder. The ECA study dealt with disorders that had occurred only in the past 6 months, but it recorded suicide attempts covering a lifetime. Thus, it is not clear whether the suicide attempts and suicidal ideation were related to panic disorder pathology.

The authors (1, 2) did find that female sex and coexisting alcohol and drug abuse increased the risk for suicide attempts in the group with panic disorder and the group with major depression. Patients with panic disorder and other comorbid psychiatric disorders were also more likely to be younger and to have never been mar-

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ried. A patient population with these characteristics (i.e., one that is primarily female, with a diversity of psychopathology including impulse disorders such as substance abuse) suggests that a coexisting *DSM-III-R* axis II disorder—borderline personality disorder—may be involved. A large-scale study (3) reported that 85% of patients with borderline personality disorder were female, and all suffered from a host of psychiatric conditions, including major depression (68%), mania (6%), bipolar disorder (11%), panic disorder (12%), alcoholism (31%), and drug use (23%).

The experience of clinicians and researchers at the anxiety and phobia clinics at the State University of New York, Health Science Center at Brooklyn, and the State University of New York at Albany suggested that patients with panic disorder with or without agoraphobia who present for treatment do not report high rates of suicidal ideation or suicide attempts. However, no formal examination of the data had been conducted. Thus, the purpose of our investigation was to examine the prevalence of fear of death, clinically significant suicidal ideation, and suicide attempts in a group of patients with *DSM-III-R* axis I panic disorder. In addition, we sought to determine whether the presence of borderline personality disorder increased the prevalence of suicidal behavior in a group of patients with panic disorder. We hypothesized that patients with panic disorder and other comorbid pathology—such as borderline personality disorder, which often includes a high rate of alcohol and drug abuse—would show a greater risk for both suicidal ideation and suicide attempts.

## METHOD

Two groups of subjects, both diagnosed as having panic disorder, were used for this study. The first group comprised 234 patients with a principal axis I diagnosis of panic disorder, with or without an axis II personality disorder other than borderline (antisocial, histrionic, avoidant, dependent, passive-aggressive, and not otherwise specified). One hundred forty-seven patients at Albany and 87 at Brooklyn met these criteria. Since Albany is the site for a number of clinical research projects on panic disorder, patients in need of crisis-oriented services were eliminated through telephone screening. At Brooklyn there is an ongoing project involving patients who have been carefully diagnosed as suffering from both panic disorder and borderline personality disorder. Therefore, the large majority of the second group of subjects for our analysis, composed of 59 patients who met the diagnostic criteria for both panic disorder and borderline personality disorder, was obtained at the Brooklyn site (N=57 at Brooklyn and N=2 at Albany).

Data were collected by a retrospective chart review of outpatients being treated by doctoral-level staff members at each clinic. All charts of patients with panic disorder and patients with panic disorder and borderline personality disorder from 1982 to the present at Brooklyn and from 1986 to the present at Albany were reviewed. Patients had originally been interviewed by experienced, doctoral-level clinicians at both sites and by advanced graduate students at Albany with the Anxiety Disorders Interview Schedule—Revised (4), a structured interview designed to assess differentially the anxiety disorders as well as the major affective disorders and substance/alcohol abuse; a brief screen is also included to rule out psychotic disorders. All interviewers had been trained to a reliability criterion by senior clinicians before doing solo interviews. At the Albany site, approximately 50% of the patients had been interviewed by an independent clinician; only those cases in which the interviewers had agreed on a principal diagnosis of panic disorder were used. The initial interviewer at Brooklyn had specifically assessed for borderline personality disorder according to the *DSM-III-R* criteria. The patient's chart had then been reviewed and a diagnosis given independently by another senior clinician at the time of the evaluation. Only cases in which both assessors had concurred were used in this study.

A 16-item standard protocol was developed for use at both clinics. The protocol assessed such variables as age, sex, marital status, length of illness, and socioeconomic status (not all data were available for all patients). Alcohol and drug histories, medical emergency room presentations, self-destructive behavior (other than suicide attempts), affective instability, perceptions of life as chaotic and/or empty, and suicide attempts were rated as either present or absent. The severity of death fears, degree of suicidal ideation, and severity of any suicide attempts were rated on 5-point Likert-type scales. Finally, self-reported frequency of panic attacks per month was included. No distinction was made between full- and limited-symptom panic attacks. Ten percent of the charts in each clinic were reviewed by a second rater for reliability estimations on certain items (thoughts of death, severity of suicidal ideation, history of suicide attempt, and severity of suicide attempt) according to the following formula: the number in agreement divided by the sum of the number in agreement and the number in disagreement. Reliability estimates for the four items were 0.80, 0.88, 0.96, and 0.96, respectively. Therefore, data obtained by the principal chart reviewers were used for all subjects.

To examine the possibility of intersite differences, chi-square analyses and t tests were conducted on all variables. No site differences emerged on any of these variables, with the exception of the axis II disorder. Therefore, all data were collapsed across sites. As we have noted, the borderline personality disorder group was almost entirely drawn from the Brooklyn site, since the Albany site routinely referred elsewhere patients who were in need of crisis-oriented services.

## RESULTS

The mean age of the patients with panic disorder was 35.3 years (SD=11.9); the mean age of the patients with

**TABLE 1. Sex and Marital Status of Patients With Panic Disorder[a] and Patients With Panic Disorder and Borderline Personality Disorder**

| Variable | Patients With Panic Disorder (N=234)[b] N | % | Patients With Panic Disorder and Borderline Personality Disorder (N=59) N | % |
|---|---|---|---|---|
| Sex | | | | |
| Male | 62 | 28 | 4 | 7 |
| Female[c] | 163 | 72 | 55 | 93 |
| Marital status | | | | |
| Never married[d] | 68 | 29 | 29 | 49 |
| Married | 128 | 55 | 12 | 20 |
| Divorced/ separated[d] | 29 | 12 | 16 | 27 |
| Widowed | 8 | 3 | 2 | 3 |

[a] With or without *DSM-III-R* axis II disorders other than borderline personality disorder.
[b] Data were not available on all variables for all subjects.
[c] Significant difference between groups ($\chi^2$=11.31, df=1, p<0.0008).
[d] Significant difference between groups ($\chi^2$=25.10, df=4, p<0.00005).

panic disorder and borderline personality disorder was 36.2 years (SD=12.0). As depicted in table 1, the two groups of subjects differed on several variables. A higher proportion of the patients with both panic disorder and borderline personality disorder were female and had never married or were separated/divorced. In addition, this group had a longer duration of illness (mean=13.7 years, SD=10.6, versus 9.9 years, SD=9.2; t=2.70, df=277, p<0.01). They were more likely to have histories of alcohol or drug abuse and more likely to present at medical emergency rooms (table 2). No differences emerged with regard to the frequency of panic attacks. The patients with panic disorder had a mean of 7.1 panic attacks (SD=7.4) in the month preceding their evaluation, and the patients with both borderline personality disorder and panic disorder had a mean of 6.2 attacks (SD=7.1) (t=0.84, df=282, n.s.).

To examine the principal hypotheses, chi-square analyses were conducted on the four items pertaining to thoughts of death (not suicidal ideation, but rather thoughts of death during a panic attack, such as fear of dying), suicidal ideation, suicide attempt, and seriousness of attempt. These data are displayed in table 3. As expected, the subjects with comorbid panic disorder and borderline personality disorder had more frequent thoughts of death. In addition, they were more likely to have clinically significant suicidal ideation and to have attempted suicide.

Other variables that are among the specific criteria necessary for a diagnosis of borderline personality disorder were subjected to chi-square analyses. These included a history of self-destructive behavior, a perception of life as chaotic and/or empty, and affective instability. Again, the results were consistent with prior hypotheses (table 2). That is, the group with panic disorder and borderline personality disorder were more likely to have histories of self-destructive behavior (other than suicide attempts), to view life as chaotic/empty, and to be affectively unstable.

Finally, we attempted to identify potential risk factors for suicidality in these two diagnostic groups. First, all variables were entered into a stepwise multiple regression analysis with pairwise deletion of missing data and suicide attempt (presence or absence) as the dependent variable. Suicidal ideation, a history of self-destructive behavior, and the frequency of panic attacks accounted for 26%, 4%, and 1.5% of the variance, respectively (F=38.13, df=3, 239, p<0.0001).

Suicidal ideation and a history of suicide attempts are almost always closely related. Since the results of this study were no different, we attempted to identify potential risk factors for suicidal ideation without entering suicide attempts into the regression analysis. The best predictors of suicidal ideation were a perception of life as chaotic/empty, affective instability, frequency of panic attacks, female sex, and self-destructive behavior (other than suicide attempts); these variables accounted for 19%, 6%, 3%, 2%, and 2% of the variance, respectively (F=21.60, df=5, 237, p<0.0001). In the stepwise regression, although diagnosis was initially the single best predictor, as other variables were added to the equation, diagnosis was removed; i.e., the other variables accounted for both diagnosis and suicidal ideation.

Although our principal hypotheses specified comparisons between the two diagnostic groups, we were also interested in potential differences between patients who had attempted suicide and those who had not. Therefore, we specifically examined these two groups without regard to diagnostic category. The mean age of the suicide attempters (N=20) was 34.5 years (SD=10.7); that of the nonattempters (N=272) was 35.6 years (SD=12.0) (t=0.46, df=22, n.s.). The mean length of illness of the suicide attempters was 12.6 years (SD=11.3); that of the nonattempters was 10.5 years (SD=9.5) (t=0.77, df=20, n.s.). As shown in table 4, patients who had made suicide attempts were more likely than nonattempters to have histories of alcohol/drug abuse, exhibit self-destructive behavior (other than suicide attempts), view life as chaotic/empty, and be affectively unstable.

## DISCUSSION

The purpose of our investigation was to assess the prevalence of suicidal ideation and suicide attempts among patients diagnosed as having panic disorder who presented for outpatient treatment. Only 2% (N=5) of our patients with panic disorder, being treated at two different sites serving a wide range of patients from different demographic and socioeconomic backgrounds, had attempted suicide, compared to 25% of the patients with panic disorder and comorbid borderline personality disorder. In addition, only 6% of the group with panic disorder reported suicidal ideation, and when concomitant clinical risk was assessed by

**TABLE 2. Psychiatric Symptoms and Histories of Patients With Panic Disorder[a] and Patients With Panic Disorder and Borderline Personality Disorder**

| Variable | Patients With Panic Disorder (N=234)[b] | | Patients With Panic Disorder and Borderline Personality Disorder (N=59)[b] | | Analysis | |
|---|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ (df=1) | p |
| Alcohol/drug abuse | | | | | 12.64 | <0.01 |
| Yes | 52 | 22 | 26 | 46 | | |
| No | 181 | 78 | 31 | 54 | | |
| Use of emergency room | | | | | 13.44 | <0.01 |
| Yes | 61 | 29 | 26 | 58 | | |
| No | 148 | 71 | 19 | 42 | | |
| Self-destructive behavior | | | | | 71.69 | <0.001 |
| Yes | 32 | 14 | 39 | 67 | | |
| No | 200 | 86 | 19 | 33 | | |
| Chaotic/empty life | | | | | 137.77 | <0.001 |
| Yes | 37 | 16 | 56 | 97 | | |
| No | 194 | 84 | 2 | 3 | | |
| Affective instability | | | | | 166.06 | <0.001 |
| Yes | 24 | 10 | 54 | 95 | | |
| No | 209 | 90 | 3 | 5 | | |

[a] With or without *DSM-III-R* axis II disorders other than borderline personality disorder.
[b] Data were not available on all variables for all subjects.

**TABLE 3. Thoughts of Death, Suicidal Ideation, and Suicide Attempts Among Patients With Panic Disorder[a] and Patients With Panic Disorder and Borderline Personality Disorder**

| Variable | Patients With Panic Disorder (N=234)[b] | | Patients With Panic Disorder and Borderline Personality Disorder (N=59) | | Analysis | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ | df | p |
| Thoughts of death | | | | | 10.10 | 4 | <0.05 |
| Not at all/infrequently | 87 | 39 | 13 | 22 | | | |
| Less than once a month | 33 | 15 | 9 | 15 | | | |
| Once a week | 25 | 11 | 13 | 22 | | | |
| 2–3 times a week | 45 | 20 | 10 | 17 | | | |
| Almost daily | 34 | 15 | 14 | 24 | | | |
| Suicidal ideation | | | | | 62.51 | 4 | <0.001 |
| Never | 173 | 75 | 19 | 32 | | | |
| Infrequently/no risk | 44 | 19 | 16 | 27 | | | |
| Frequently/no risk | 9 | 4 | 8 | 14 | | | |
| Frequently/at some risk | 4 | 2 | 14 | 24 | | | |
| Frequently/severe risk | 1 | 0.4 | 2 | 3 | | | |
| History of suicide attempt | | | | | 39.98 | 1 | <0.001 |
| Yes | 5 | 2 | 14 | 25 | | | |
| No | 228 | 98 | 45 | 75 | | | |
| Seriousness of suicide attempt | | | | | 133.13 | 2 | <0.01 |
| Very insignificant | 1 | 0.5 | 7 | 12 | | | |
| Very significant | 4 | 2 | 7 | 12 | | | |

[a] With or without *DSM-III-R* axis II disorders other than borderline personality disorder.
[b] Data were not available on all variables for all subjects.

trained mental health interviewers, the rate was 2%. Forty-one percent of the group with panic disorder and borderline personality disorder reported frequent suicidal ideation, with 27% considered to be at clinical risk. The low rate of suicide attempts among patients with panic disorder is consistent with that reported by Beck et al. (5). In their retrospective study of 900 outpatients in various diagnostic categories, only one patient among 151 with panic disorder reported a previous suicide attempt. In contrast, they found that 7% of the patients diagnosed as having a mood disorder reported a suicide attempt.

The results of this study and that of Beck et al. (5) differ substantially from those of Weissman and associates (1, 2). In their sample, 47% of the patients with panic disorder contemplated suicide, while 44% "felt

**TABLE 4. Characteristics of Patients With Panic Disorder With or Without Borderline Personality Disorder Who Did or Did Not Attempt Suicide**

| Variable | Patients Who Attempted Suicide (N=20) |  | Patients Who Did Not Attempt Suicide (N=272)[a] |  | Analysis |  |  |
|---|---|---|---|---|---|---|---|
|  | N | % | N | % | $\chi^2$ | df | p |
| Sex |  |  |  |  | 1.98 | 1 | n.s. |
| Male | 2 | 10 | 63 | 25 |  |  |  |
| Female | 18 | 90 | 203 | 75 |  |  |  |
| Alcohol/drug abuse |  |  |  |  | 8.50 | 1 | <0.04 |
| Yes | 11 | 55 | 68 | 25 |  |  |  |
| No | 9 | 45 | 204 | 75 |  |  |  |
| Self-destructive behavior |  |  |  |  | 42.08 | 1 | <0.001 |
| Yes | 17 | 85 | 55 | 20 |  |  |  |
| No | 3 | 15 | 217 | 80 |  |  |  |
| Chaotic/empty life |  |  |  |  | 21.76 | 1 | <0.0001 |
| Yes | 16 | 80 | 79 | 29 |  |  |  |
| No | 4 | 20 | 191 | 71 |  |  |  |
| Affective instability |  |  |  |  | 20.60 | 1 | <0.001 |
| Yes | 14 | 70 | 64 | 24 |  |  |  |
| No | 6 | 30 | 208 | 76 |  |  |  |
| Thoughts of death |  |  |  |  | 8.18 | 4 | <0.08 |
| Not at all/infrequently | 6 | 30 | 95 | 36 |  |  |  |
| Less than once a month | 0 | 0 | 43 | 16 |  |  |  |
| Once a week | 2 | 10 | 36 | 14 |  |  |  |
| 2–3 times a week | 5 | 25 | 50 | 19 |  |  |  |
| Almost daily | 7 | 35 | 41 | 16 |  |  |  |
| Suicidal ideation |  |  |  |  | 86.04 | 4 | <0.0001 |
| Never | 0 | 0 | 192 | 71 |  |  |  |
| Infrequently/no risk | 7 | 35 | 55 | 20 |  |  |  |
| Frequently/no risk | 2 | 10 | 15 | 6 |  |  |  |
| Frequently/at some risk | 9 | 45 | 9 | 3 |  |  |  |
| Frequently/severe risk | 2 | 10 | 1 | 0.4 |  |  |  |

[a] Data were not available on all variables for all subjects.

like [they] wanted to die." However, as previously discussed, ratings were made by trained lay interviewers, without any apparent attempt to assess clinical risk. Moreover, 64% of the subjects in their sample purportedly "thought a lot about death." This can be compared to 61% of the group with panic disorder and 78% of the group with both panic disorder and borderline personality disorder in our study who had thoughts of death. The frequencies reported in our study were obtained by examining the presence and severity of fear of dying and thoughts of death during panic attacks; suicidal ideation was not included in this rating.

It must be noted that the frequency of a history of suicide attempts of patients with panic disorder in this study (2%) is still higher than the 1% found in an epidemiologic study of persons without any psychiatric disorder (1, 2). In addition, the rate of suicidal ideation that was judged to be of clinical severity in our patients with panic disorder (2%) needs to be compared to the results of the reanalysis of the ECA study (1, 2), in which it was found that 15% of persons without any psychiatric disorder "thought a lot about death" and 4% of these persons responded positively to the statement "Felt so low, thought about committing suicide."

It should also be noted that individuals with panic disorder who fear losing control occasionally have thoughts that they could die as a consequence (e.g., losing control during a panic attack and driving off a bridge). However, current clinical experience suggests that this is what patients fear and that it must be distinguished from suicidal wishes and/or intent. Thoughts of death in a sample of individuals with panic disorder is not surprising; indeed, it is expected.

There may be several additional explanations for our findings and their discrepancy with those previously reported (1, 2). First, the method of assessment and the type of interviewer differed. Chart reviews on clinical patients, as done in this study, are different from a prospective epidemiologic survey and clearly may tap different patient populations.

Sample characteristics represent a second difference in these two studies. The characteristics of individuals at risk for suicide in the ECA study (1, 2) were very similar to those of our group with panic disorder and borderline personality disorder. That is, subjects at risk in both studies were young women with histories of alcohol/drug abuse. In addition, our subjects with histories of suicide attempts also described their lives as chaotic and/or empty, exhibited other self-destructive behavior, and had a great deal of affective instability. At the Albany site, if patients over the telephone described imminent suicidal ideation and/or behavior they were referred elsewhere, thereby accounting for the small number of patients with panic disorder and borderline personality disorder at Albany.

The degree of psychopathology and the psychiatric histories of the subjects in these studies are other potentially important variables. Our subjects consisted entirely of help-seeking outpatients. Less than 5% of our subjects in both the group with panic disorder and the group with panic disorder and borderline personality disorder had histories of psychiatric hospitalization. In the ECA study, although lifetime psychiatric history was assessed, it was not reported fully. In fact, the report (1) clearly stated that both the panic disorder and panic attack groups "may have had other psychiatric disorders in the past." Unfortunately, data on the proportion of individuals with other disorders in the past and the nature of such disorders were not available. Consequently, one cannot discern whether individuals who reported suicidal ideation and/or suicide attempts had suffered previously from other serious psychopathology that might have contributed to suicidality. While not denying the clinical impairment and severity of distress that patients with panic disorder may experience, one cannot rule out the hypothesis that a history of other psychiatric disorders increased the distress level beyond tolerance, so that suicide became a viable option. In fact, in the present study, the regression analysis found that perception of life as chaotic, affective instability, frequency of panic attacks, female sex, and a history of self-destructive behavior were the best predictors of suicidal ideation. Similar findings have been noted by others (5–7). Clearly, cross-validation of our findings with another sample is warranted.

Finally, the sample of Weissman et al. (1) consisted of a random assortment of community members. Thus, subjects surveyed may have included individuals who not only were untreated for panic disorder but also were unaware of the possibility of treatment for this disorder. As a consequence, they may have been particularly demoralized and helpless, resulting in a high frequency of suicidal ideation and/or suicide attempts. As Johnson et al. (2) cogently argued, the low rate of suicidality observed in clinical samples may be due to the low base rate of suicidal behavior. Lifetime analyses may be better equipped to identify such patterns.

The experience of panic disorder is distressing and is responsible for considerable help-seeking behavior and decreased quality of life. Individuals with panic disorder experience a significantly impaired quality of life, as measured by alcohol/drug abuse, time with friends and relatives, time spent on hobbies and social activities, marital functioning, and financial dependency (6). Panic disorder is often responsible for inappropriate and expensive utilization of medical resources (7). However, the results of our investigation, though certainly not conclusive, are not consistent with previous assertions that individuals with panic disorder are at a directly greater risk for suicidal ideation, suicide attempts, or possibly suicide simply by virtue of that diagnosis. Rather, the results of this and other investigations suggest that the suicidal behavior evidenced by individuals suffering from panic disorder or panic attacks may be due to the existence of other axis I disorders and/or borderline personality disorder. In addition, panic attacks and/or panic disorder may lead to an increase in alcohol and substance abuse, emergency room visits, and a decrease in overall quality of life, which may ultimately lead to such demoralization and hopelessness that the patients are then at greater risk for suicide (8–10). Further studies are needed to determine the precise conditions under which an individual with panic disorder is at greater risk for suicide.

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# Low Cerebellar Metabolism in Medicated Patients With Chronic Schizophrenia

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*Because of the frequent association of cerebellar structural defects with schizophrenia, the authors reanalyzed the metabolic brain images of patients with chronic schizophrenia to assess if they had abnormalities in cerebellar metabolism. They used carbon-11-2-deoxyglucose and positron emission tomography to study 18 medicated patients with chronic schizophrenia and 12 normal comparison subjects. Patients with schizophrenia showed significantly lower absolute and relative metabolism in the cerebellum than normal subjects.*

(Am J Psychiatry 1992; 149:686–688)

The role of the cerebellum in the pathogenesis of schizophrenia is controversial. Cerebellar atrophy in patients with schizophrenia has been documented by computerized tomography (CT) and magnetic resonance imaging (MRI) (1–5), and post-mortem studies have revealed pathological changes in the cerebellum of patients with chronic schizophrenia (6–8). However, other investigators have failed to document cerebellar atrophy in patients with chronic schizophrenia (9–12). Measurement of regional brain glucose metabolism with positron emission tomography (PET) has been shown to be a sensitive technique to demonstrate regional brain changes associated with mental illnesses (13) and may be able to detect abnormalities that cannot be documented with either CT or MRI (14). The purpose of this study was to find out if there were cerebellar metabolic abnormalities in a group of patients with chronic schizophrenia in whom we had previously documented defects in the frontal cortex and basal ganglia (15) but whose cerebellar regions we had not analyzed.

## METHOD

Twelve normal volunteers (23–47 years of age) and 18 medicated patients who fulfilled both *DSM-III* criteria and Research Diagnostic Criteria for chronic schizophrenia (22–41 years of age) were studied. The patients were recruited from an urban psychiatric hospital; 12 were in the last phases of their hospitalization, and six were discharged within 1 week of completion of the study. The clinical and demographic characteristics of the normal subjects and the patients with schizophrenia have been described elsewhere (16). The mean age of the patients was 29 years (SD=7), and they had been using neuroleptics for a mean of 7 years (SD=5). The patients' mean scores on the Brief Psychiatric Rating Scale (BPRS) are given in table 1.

Brain glucose metabolism was assessed during baseline conditions by using PET and [1-$^{11}$C]2-deoxy-D-glucose (carbon-11-2-deoxyglucose) as described elsewhere (16). Regions for the left and right cerebellum were delineated on two contiguous planes of the individual's CT scan images. These regions were then projected onto the corresponding planes of the PET scan images. A weighted average was then obtained to com-

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**TABLE 1. BPRS Scores of 18 Patients With Chronic Schizophrenia[a]**

| | Score | |
|---|---|---|
| BPRS Scale | Mean | SD |
| Somatic preoccupation | 2.1 | 1.1 |
| Anxiety | 3.3 | 1.0 |
| Emotional withdrawal | 3.0 | 1.3 |
| Conceptual disorganization | 3.4 | 0.8 |
| Guilt feelings | 1.3 | 0.7 |
| Tension | 2.9 | 1.2 |
| Mannerisms | 2.6 | 1.2 |
| Grandiosity | 1.9 | 1.0 |
| Depressive mood | 2.0 | 1.2 |
| Hostility | 2.5 | 1.4 |
| Suspiciousness | 3.6 | 1.5 |
| Hallucinations | 3.3 | 1.4 |
| Motor retardation | 2.1 | 1.6 |
| Uncooperativeness | 1.3 | 1.0 |
| Unusual thought content | 3.8 | 1.1 |
| Blunted affect | 3.5 | 1.3 |
| Excitement | 1.5 | 0.8 |
| Disorientation | 1.1 | 0.5 |

[a]BPRS ratings were performed within 1 week of the PET scan.

**TABLE 2. Absolute and Relative Metabolic Values for Left and Right Cerebellum in 12 Normal Subjects and 18 Medicated Patients With Chronic Schizophrenia[a]**

| | Cerebellar Metabolic Value | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Absolute (μmol/100 g/min) | | | | Relative | | | |
| | Left | | Right | | Left | | Right | |
| Subjects | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Normal subjects (N=12) | 37.9 | 5 | 37.5 | 4 | 1.00[a] | 0.07 | 1.05 | 0.06 |
| Patients with schizophrenia (N=18) | 32.8 | 4 | 32.6 | 4 | 0.99 | 0.07 | 0.99 | 0.07 |

[a]Weighted averages were obtained to compute absolute metabolic values; cerebellar values were divided by whole brain metabolism to compute relative values. Two-group repeated-measures analysis of variance showed no Group by Left-Right interaction and no left-right differences but did show significantly lower overall absolute values (F=9.7, df=1, 28, $p\leq0.005$) and relative values (F=5.3, df=1, 28, $p\leq0.05$) in patients with schizophrenia.

pute the "absolute" metabolic values of the left and right cerebellum. To normalize for differences in whole brain metabolism between subjects, we also obtained "relative" measures by dividing cerebellar values by whole brain metabolism (16). Whole brain metabolism was the average metabolic activity in the 10 central slices. Differences on the absolute and relative cerebellar metabolic values between normal subjects and patients with schizophrenia were tested with a two-group repeated-measures analysis of variance (ANOVA).

Since frontal and cerebellar metabolism have been shown to be correlated (17–19) and we had previously shown that the patients investigated in this study had low relative and absolute frontal metabolism (15), we assessed the correlation between the metabolic values for the cerebellum and the frontal cortex using Pearson correlation coefficients. We also investigated the relation between cerebellar and basal ganglia metabolism because these two structures are neuroanatomically connected (20), and we had also documented significantly higher relative metabolism of the basal ganglia in these patients (15). Relative measures were chosen for the correlation analyses because these measures are better suited to investigate regional patterns of interaction than the absolute metabolic values (16).

## RESULTS

Table 2 shows the absolute and relative metabolic values for left and right cerebellum of the normal subjects and the patients with schizophrenia. The two-group repeated-measures ANOVA showed no Group by Left-Right interaction and no left-right differences but did show an overall difference between normal subjects and patients with schizophrenia for absolute and relative cerebellar metabolism.

There were no significant correlations between the relative metabolic values of the cerebellum and those of the frontal cortex (left cerebellum r=0.19, df=29, n.s.; right cerebellum r=0.05, df=29, n.s.) or between the relative metabolic values of the cerebellum and those of the basal ganglia (left cerebellum r=0.26, df=29, n.s.; right cerebellum r=0.27, df=29, n.s.).

## DISCUSSION

This preliminary study provides evidence of lower cerebellar metabolism in medicated patients with chronic schizophrenia than in normal comparison subjects. The implication of this finding with respect to the pathophysiology of schizophrenia is unclear because these patients were taking medication at the time of the study. Lower cerebellar metabolism could relate to the effects of chronic neuroleptic treatment. Although one could argue that the absence of dopamine receptors in the cerebellum would make it insensitive to the actions of dopamine antagonists, one must consider the neuroanatomical connections between the cerebellum and the basal ganglia (20). In fact, animal studies have shown increases in cerebellar glucose metabolism after administration of dopamine agonists (21) and decreases in cerebellar metabolism after administration of dopamine antagonists (22). However, since there is evidence that patients with schizophrenia have abnormalities in dopamine brain activity, lower cerebellar metabolism could also reflect these defects.

One also needs to consider the relationship between frontal and cerebellar metabolism (17–19) in the interpretation of these findings. However, the fact that there were no significant correlations between relative metabolic activity in the cerebellum and in the frontal cortex argues against the notion that the lower cerebellar metabolism is a reflection of the abnormal frontal metabolic activity seen in these patients (16).

Similarly, there were no significant correlations between relative metabolic activity in the cerebellum and in the basal ganglia, suggesting that the cerebellar metabolic changes may be independent of the frontal and subcortical defects seen in these patients.

This study documents cerebellar metabolic abnormalities in medicated patients with chronic schizophrenia. Studies on never-medicated patients with schizophrenia are required to rule out whether the findings in this report are related to chronic use of neuroleptics or to the schizophrenic process itself.

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# Weight Gain Among Schizophrenic Patients Treated With Clozapine

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*A retrospective chart review was used to assess weight changes in 36 chronic schizophrenic inpatients who were treated with clozapine after being treated with standard neuroleptics. The average weight gain during 6 months of clozapine treatment was 16.9 lb; 75.0% of the patients gained at least 10 lb. The results confirm previous findings of clozapine-associated weight gain.*

(Am J Psychiatry 1992; 149:689–690)

Clozapine is the first antipsychotic medication that has been proven superior to standard neuroleptics for treatment-refractory schizophrenia. Depending on how treatment resistance is defined, potential candidates for clozapine therapy in the United States may number in the hundreds of thousands. Clozapine causes fewer extrapyramidal side effects than neuroleptics but has a variety of other side effects, including weight gain. While obesity is a known health risk and has been documented as a side effect of neuroleptics (1, 2), the degree of weight gain associated with clozapine is unclear. In a review of more than 13,000 patients treated with clozapine worldwide, Lieberman et al. (3) reported weight gain in 0.73%. In a retrospective review of the medical charts of 503 inpatients, Naber and Hippius (4) noted weight gain in only three patients. However, Povlsen et al. (5) noted a frequency of 11.6% in a retrospective study of 216 inpatients treated with a mean daily dose of 317 mg for up to 12 years. Taken together, these reports have suggested that weight gain occurs infrequently during clozapine treatment.

In contrast, Leadbetter et al. (6) recently reported that 38% of their group of 21 chronically mentally ill patients gained over 10% of their body weight during clozapine treatment. Also, Cohen et al. (7) have described significant weight gain in seven schizophrenic patients treated with clozapine. Six of these patients gained an average of 24.7 lb, and the authors concluded that clozapine may be associated with the same degree of weight gain seen with typical neuroleptics.

The purpose of the present study was to examine the frequency and magnitude of weight gain in clozapine-treated chronic schizophrenic patients. This study involved a retrospective review of hospital charts for a group of patients treated with both neuroleptics and clozapine.

## METHOD

Our subjects were 36 inpatients in a state hospital who were consecutively treated with clozapine over 33 months. All patients had clinical diagnoses of chronic schizophrenia, according to *DSM-III-R* criteria, with a variety of subtypes. The mean length of the current hospitalization was 8.2 years (SD=7.6), and the mean number of previous hospitalizations was 5.8 (SD=3.1). Twenty-seven (75.0%) of the subjects were male, and the mean age of the total group was 34.8 years (SD=9.3). The patients were selected for clozapine treatment by their attending psychiatrists because they had shown little or no clinical improvement during adequate trials of at least three different neuroleptics in the previous 5 years. The mean total duration of neuroleptic treatment during the current hospitalization was 6.8 years (SD=4.8). The neuroleptic treatment received by the group during the 6 months before clozapine treatment is summarized in table 1. Neuroleptics were discontinued, and the patients' mean clozapine dose was 380 mg/day (SD=135). The transition from neuroleptics to clozapine was made without a washout period and was generally completed within 4–6 weeks.

Each patient was weighed monthly during the last 6

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**TABLE 1. Standard Neuroleptics Received by 36 Chronic Schizophrenic Inpatients During 6 Months Before Clozapine Treatment**

| | | Dose (chlorpromazine equivalents/day) | | Duration (days) | |
|---|---|---|---|---|---|
| Neuroleptic[a] | N | Mean | SD | Mean | SD |
| Haloperidol | 11 | 1519.5 | 781.0 | 110.2 | 57.7 |
| Fluphenazine | 8 | 1375.0 | 860.0 | 106.6 | 65.4 |
| Thiothixene | 11 | 1083.4 | 285.2 | 114.2 | 57.9 |
| Trifluoperazine | 9 | 944.4 | 481.0 | 98.1 | 63.08 |
| Perphenazine | 1 | 100.0 | | 91.0 | |
| Loxapine | 1 | 800.0 | | 118.0 | |
| Chlorpromazine | 5 | 820.0 | 465.4 | 134.0 | 46.51 |
| Thioridazine | 4 | 558.3 | 252.4 | 90.5 | 30.5 |

[a]Patients received up to three different neuroleptics each.

months of neuroleptic treatment and the first 6 months of clozapine treatment. Clozapine treatment was initiated during fall and winter months for 15 (41.7%) of the patients, and for 21 (58.3%) it began during spring and summer months. Patients were weighed in street clothes before breakfast and had unrestricted access to food and physical activity throughout the study. An ideal weight range, including minimum and maximum ideal weights, was calculated for each patient by a registered dietitian. Weight change was assessed by comparing the patient weights before and after each 6-month treatment period. The score on the Brief Psychiatric Rating Scale (BPRS) was also determined by each patient's attending psychiatrist every 6 weeks during clozapine treatment.

## RESULTS

The group showed stable weight during the 6 months of standard neuroleptic treatment (mean weight change= –0.2 lb, SD=11.0). When clozapine treatment began, seven (19.4%) of the patients weighed less than their minimum ideal weights and 23 (63.9%) weighed more than their maximum ideal weights. As a group they weighed an average of 15.3 lb (SD=35.3) more than their maximum ideal weights. The group subsequently gained an average of 16.9 lb (SD=10.9) during the 6 months of clozapine treatment ($t=9.33$, $df=35$, $p<0.0001$, paired t test). Expressed as a percentage of maximum ideal weight, the mean weight gain for each patient during clozapine treatment was 10.6% (SD=6.8%). Of the 36 patients, 27 (75.0%) gained at least 10 lb while taking clozapine, and 15 (41.7%) gained at least 20 lb. The mean BPRS score dropped from 66 (SD=15) to 47 (SD=16) during the 6 months of clozapine treatment ($t=10.25$, $df=29$, $p<0.0001$, paired t test). We noted a tendency for this change to correlate inversely with the amount of weight gained during clozapine treatment (Spearman $r=-0.31$, $df=28$, $p<0.10$). BPRS scores were not available for six patients.

## DISCUSSION

This study demonstrates significant weight gain in a group of schizophrenic patients during clozapine treatment. Weight gain associated with standard neuroleptics has been reported to plateau after 1 to 2 years of treatment (1). Since the group in our study had been maintained on neuroleptics an average of 6.8 years, this possibility would explain our failure to find a significant weight change during the neuroleptic treatment period. The patients averaged 15.3 lb over their maximum ideal weights before receiving clozapine, suggesting that clozapine treatment exacerbated a preexisting problem in the group.

The mechanism of clozapine-associated weight gain remains uncertain. Discussing neuroleptic-associated weight gain, Brady (2) noted that the mechanism is likely to be multifactorial. Possibilities include drug effects on serotonergic, anticholinergic, and histaminic neurotransmitter systems, in addition to effects on endocrine and metabolic functions.

Published estimates of the degree of weight gain associated with neuroleptics have varied widely, making comparison with clozapine difficult. Reviewing this literature, Amidsen (1) concluded that an average weight gain of 6.6 to 11 lb is usual after 6 months of neuroleptic treatment. Ability to induce weight gain has also been reported to vary inversely with neuroleptic milligram potency (2). In a recent study directly comparing fluphenazine and clozapine, Konicki et al. (8) found significantly greater weight gain with clozapine. Considered with the results of the present study, those data suggest that clozapine could cause more weight gain than many standard neuroleptics. Since prevention may be the best strategy in managing antipsychotic-induced weight gain (2), physicians should be aware of this side effect when prescribing clozapine.

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# CSF Cholecystokinin Concentrations in Patients With Panic Disorder and in Normal Comparison Subjects

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*Cholecystokinin concentrations in the CSF of 25 patients with panic disorder and 16 normal comparison subjects were ascertained by radioimmunoassay. The patients with panic disorder had significantly lower CSF concentrations of cholecystokinin, which may reflect increased CNS cholecystokinin receptor sensitivity, reduced numbers of receptors, or a compensatory reduction in cholecystokinin octapeptide secondary to theoretically increased central cholecystokinin tetrapeptide activity.*

(Am J Psychiatry 1992; 149:691–693)

Cholecystokinin is a neuroactive peptide that exists in various forms and exhibits a variety of peripheral and CNS actions (1, 2). Cholecystokinin octapeptide (CCK-8) is believed to be the most prevalent form of cholecystokinin in the CNS (1, 2). It appears that CCK-8 and various analogues may modulate CNS dopamine neurotransmission, and they have been studied as potential antipsychotic agents (2). Animal studies indicate a functional antagonism between CCK-8 and benzodiazepines in hippocampal cells (3), and recent studies suggest that in "anxious" rats, the numbers of CCK-8 receptors are reduced in the hippocampus (4). Measurement of CSF cholecystokinin in patients with schizophrenia, mood disorders, eating disorders, and Parkinson's disease has produced inconsistent results (2).

Interesting work by de Montigny (5) and Bradwejn et al. (6) has indicated that cholecystokinin in the tetrapeptide form (CCK-4) is a potent anxiogenic agent. In patients with panic disorder, CCK-4 appears to have potent panicogenic properties with minimal gastrointestinal effects. In a recent study (7), 10 (91%) of 11 panic disorder patients experienced panic attacks, compared to two (17%) of 12 normal control subjects, after injections of 25 μg of CCK-4.

To investigate possible abnormalities in CNS cholecystokinin in patients with anxiety disorders, we analyzed the CSF of 25 patients with panic disorder and 16 comparison subjects for cholecystokinin immunoreactivity.

## METHOD

The patients with panic disorder were five men and 20 women between the ages of 18 and 65 years (mean=35.6 years, SD=8.8) who were in good physical health and had given verbal and written consent. They were evaluated by means of the Structured Clinical Interview for DSM-III (SCID) (8) and met the *DSM-III* criteria for panic disorder or agoraphobia with panic attacks. Patients with major depression were included only if their panic disorder symptoms had preceded the onset of major depression and depression was not the principal diagnosis. Patients with melancholia were excluded, as were patients with other axis I disorders.

The normal comparison subjects (eight male and eight female; mean age=30.0 years, SD=7.7) were recruited by advertisement. They were also interviewed with the SCID and were found to be free of any axis I psychiatric diagnosis. In addition, no first-degree relative of the normal comparison subjects had a psychiatric diagnosis (according to patient history).

The patients and comparison subjects were admitted to our clinical research center the night before the CSF sampling procedure was done. All subjects had been maintained on a low-monoamine diet for the previous 4 days, had had at least 9 hours of bed rest, and had fasted overnight prior to the procedure. Lumbar CSF was obtained between 8:00 and 10:00 a.m., immediately frozen on dry ice, and stored at –70 °C until assay. Total cholecystokinin immunoreactivity was assayed by radioimmunoassay (9) in aliquots from a pool of CSF (12th–25th cc). Samples were assayed by using

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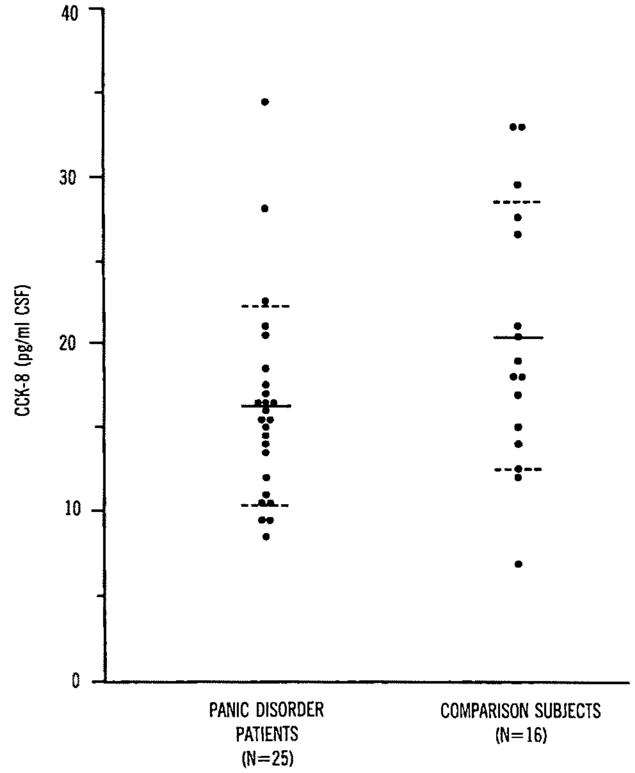
**FIGURE 1. CSF Cholecystokinin Concentrations in Patients With Panic Disorder and in Normal Comparison Subjects**[a]



[a] Solid lines are means; dashed lines are standard deviations.

200-μl aliquots in duplicate and averaging results. Results are expressed in picograms per milliliter.

## RESULTS

The group of patients with panic disorder did not differ significantly in age, height, weight, or sex from the group of normal comparison subjects. Eight of the patients with panic disorder also met the criteria for current major depression. The patients had been asked to remain medication free for 2 weeks before the procedure. Of the 25 patients, 17 had been medication free for at least 2 weeks (mean=8 weeks, range=2–28), five never took medication, and three had been medication free for 1–2 weeks (one patient had been taking diazepam, 5 mg p.r.n.; one had been taking amitriptyline, 25 mg/day; and one had been taking clorazepate, 7.5 mg/day). Five patients had taken a dose of a benzodiazepine between 2 and 7 days before the procedure (four took diazepam, 5 mg, and one took lorazepam, 1 mg).

The CCK-8 immunoreactivity of both groups is shown in figure 1. The CCK-8 concentrations in the comparison group were normally distributed. Concentrations did not differ between the men (mean=20.5 pg/ml, SD=7.3) and the women (mean=20.5 pg/ml, SD=8.5) in the normal comparison group or between the male patients (mean=15.3 pg/ml, SD=4.0) and the female patients (mean=16.5 pg/ml, SD=6.5). However, the difference between the CCK-8 levels of the comparison group (mean=20.6 pg/ml, SD=7.7) and the patient group (mean=16.2 pg/ml, SD=5.9) was analyzed with Student's t test and found to be significant (t=2.05, df=39, p<0.05). The subgroup of patients with panic disorder and major depression did not differ from the nondepressed patients with panic disorder with respect to CCK-8 concentrations.

Concentrations of CCK-8 in the CSF of the patients who had taken benzodiazepines within 1 week of the procedure (mean=16.3 pg/ml, SD=2.0) were not different from those of the rest of the patient group (mean=16.0 pg/ml, SD=6.5) (t=0.11, df=23, n.s.). CSF levels of CCK-8 in patients who had ever been treated with benzodiazepines (N=14) and those who had never taken them (N=11) were not significantly different (mean=18.7 pg/ml, SD=7.5, versus 14.2 pg/ml, SD=4.5; t=1.64, df=23, n.s.).

## DISCUSSION

To our knowledge, this is the first report of CSF cholecystokinin concentrations in patients with panic disorder. In this study, CSF cholecystokinin concentrations were significantly lower in patients with panic disorder than in normal comparison subjects, an unexpected finding. It is possible that cholecystokinin receptor sensitivity is increased in patients with panic disorder and that what we observed was a compensatory reduction in cholecystokinin activity which may occur as a secondary phenomenon. Alternatively, this finding may be a reflection of a reduced number of brain cholecystokinin receptors in these patients, with a concomitant lowering of central CCK-8 activity. In rodents, in vitro studies have shown that pretreatment of cell preparations with CCK-4 will prevent CCK-8-induced neuronal firing, suggesting that there may be some antagonistic interaction between the two forms (10). Our data may reflect indirectly an increase in CNS CCK-4 activity with a compensatory decrease in CCK-8 activity.

In the several previous reports (2), there were variable findings on CSF cholecystokinin activity in patients with various psychiatric and neurological disorders compared to normal subjects, suggesting that lowered cholecystokinin levels are not necessarily a nonspecific finding across various patient samples. Interestingly, recent evidence suggests that chronic diazepam treatment produces variable region-specific changes in cholecystokinin receptor density in rodents (11). Medication treatment history did not appear to have affected cholecystokinin measurements in our patients, although the effects of prior treatment with, or current surreptitious use of, benzodiazepines still cannot be ruled out completely. All of the patients in our study who used benzodiazepines within 1 week of testing did so to control their anxiety about coming to the hospital. None took other medication regularly during the 2 weeks before the procedure. It is likely that the four patients who took diazepam prior to hospitalization still had some residual benzodiazepine at the time of CCK-8 sampling. To the best of our knowledge, however, this did not affect our findings.

Finally, since the numbers of patients and comparison subjects were relatively small, replication of these preliminary data in a larger group is indicated. There is no known CSF concentration gradient for cholecystokinin; our use of similar pools for each sample obviates this potential technical problem. As further information regarding the distribution of cholecystokinin receptors in the human CNS becomes available, and as interaction with other monoamine and neuropeptide systems is further elucidated, additional light may be shed on the potential role of cholecystokinin in the CNS of normal subjects and patients with anxiety disorders.

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# Abnormal Diurnal Variation in Circulating Natural Killer Cell Phenotypes and Cytotoxic Activity in Major Depression

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*This investigation tested the hypothesis that depressed patients have abnormal diurnal variation of natural killer (NK) cell measures. The diurnal variation of levels of Leu-11 NK cells and NK cytotoxic activity was significantly less in 24 patients with major depression than in 24 normal comparison subjects. These findings provide evidence that aspects of immune, as well as neural and endocrine, chronobiology are abnormal in depression.*

(Am J Psychiatry 1992; 149:694–696)

Since the classic clinical investigation by Sachar et al. (1), which showed abnormal 24-hour patterns of cortisol secretion in psychotic depression, advances in the research of biological rhythms have led to new insights into the pathophysiology of affective illness. Disturbances in the circadian rhythms of several neurobiological measures—including noradrenergic activity, cortisol, melatonin, thyrotropin, temperature regulation, and the sleep-wake cycle—have been associated with major affective syndromes (2). Important components of the cellular immune system in both animals and humans also exhibit normal chronobiological patterns of activity, and considerable evidence from basic and clinical studies has established that the CNS plays a key role in modulating various aspects of immune system function (3). While the endogenous pacemakers that govern immunological rhythms are not yet understood, it has been posited that immune bioperiodicity may be entrained to rhythms of CNS origin (4).

Natural killer (NK) cells are a heterogeneous subset of large granular lymphocytes that show cytotoxicity which is not restricted by the major histocompatibility complex. These cells are believed to be involved in the natural resistance to tumor growth and microbial infection and in other important immunoregulatory functions, such as the production of lymphokines (5). Several recent clinical investigations have demonstrated that circulating NK activity (in the morning) is abnormally low in depression (6), and to date this observation has been the most reproducible abnormality in cellular immunity associated with major depression. We recently reported (7) that low circulating levels of the Leu-11 (CD16) NK cell phenotype accompany low NK activity in depressed subjects and may be one important immunological mechanism by which NK activity is impaired in depression. Basic studies provide evidence that NK activity may be regulated by neural (e.g., noradrenergic, GABA-ergic) and endocrine (e.g., corticotropin-releasing factor, ACTH, cortisol, β-endorphin) modulators, which have been implicated in the neurobiology of depression (3). Thus, several lines of evidence suggest that abnormalities in the diurnal variation in some mediators of CNS function associated with depression may lead to perturbations in the normal diurnal variation of NK cell measures. To date, however, there have been few data on such a relationship in affective disorders. To test the hypothesis that NK cell diurnal variation is abnormal in depression, we examined circulating NK cell phenotypes and NK activity in subjects with major depression and in normal comparison subjects at both 8:00 a.m. and 4:00 p.m. on the same day. These times were chosen because 8:00 a.m. and 4:00 p.m. have been shown to approximate the diurnal peak and nadir, respectively, of NK cell activity in healthy, normal individuals (on a schedule of nocturnal rest and diurnal activity) (8). To our knowledge, this is the first study to show that the diurnal variation of a measure of cellular immunity is abnormal in patients with major depression.

## METHOD

Forty-eight subjects participated in this study: 24 inpatients with major depression and 24 healthy, normal comparison subjects. All subjects provided written informed

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consent. These subjects were part of a substantially larger study of depression and immune function (7) and are the subset of subjects from whom both 8:00 a.m. and 4:00 p.m. blood samples for NK determinations were obtained on the same day. As closely as possible, the comparison subjects were matched to the patients with major depression for mean age and sex distribution: mean age=30.9 years (SD=7.8) and 30.5 years (SD=8.8), respectively; percentage of men=67% and 58%. The diagnoses were assigned by a board-certified research psychiatrist (D.L.E.) on the basis of all available clinical information and data obtained with the Schedule for Affective Disorders and Schizophrenia (SADS). The comparison subjects were recruited by means of printed advertisement. The mean scores on the 17-item Hamilton Rating Scale for Depression were 16.2 (SD=8) for the subjects with major depression and 0.8 (SD=2) for the comparison subjects. The subjects were on a schedule of nocturnal rest and diurnal activity and were free of all medications with known or suspected immune effects (e.g., psychotropics—including antidepressants—anticonvulsants, antihistamines, antihypertensives, steroids, anti-inflammatory drugs, antibiotics) for at least 2 weeks before testing. The immune assays were performed blind to diagnosis, and all diagnoses were made blind to the results of the immune assays.

The NK cell phenotyping and NK activity determinations were performed with standard methods previously described (7). Briefly, Leu-7 (HNK-1) and Leu-11 (CD16) lymphocytes were identified by using Leu series monoclonal antibodies and were counted with a fluorescence-activated flow cytometer. Single-color staining was employed for the determination of the percentage of Leu-7 large granular lymphocytes (percentage of lymphocytes, $10^6$ cells/ml), and two-color staining was used in this investigation to determine the percentage of Leu-11a,c positive lymphocytes (percentage of lymphocytes, $10^6$ cells/ml); the latter are the predominant population of NK active effector cells in humans. Whereas previous chronobiological investigations of NK cell phenotype levels among normal subjects have been conducted with older, less selective monoclonal antibodies (5), this is the first investigation of which we are aware that uses the anti-Leu-11 monoclonal antibody to assess the diurnal variation of NK cell levels. NK activity determinations were performed for a subset of patients (18 depressed patients, 11 comparison subjects) with chromium-labeled, NK-sensitive K562 tumor cells as the target. The percentage of specific lysis of tumor targets at each of five effector/target cell ratios (12.5 to 200:1), the area under the concentration-response curve, and the mean NK activity (the average of the five effector/target cell ratios) were calculated for each subject.

For the individual dependent immune variables examined, a difference score was computed for each subject (4:00 p.m. value minus 8:00 a.m. value). Any potential variance in the dependent immune variables due to age or gender was controlled for in all statistical analyses. Analysis of covariance (ANCOVA), covarying for age and gender, was used to test for differences between the patients with major depression and the normal comparison subjects, and Pearson partial correlations were performed to examine the relationship between Hamilton severity rating and diurnal variation for each immune measure. For statistical analyses, immune values were log-transformed to normalize group variance. Adjusted logged values were unlogged for presentation in the text. The mean and standard deviation are reported, and two-tailed tests were used throughout. The group differences in diurnal variation of the dependent immune variables reported are computed difference scores analyzed by ANCOVA.

## RESULTS

Statistical analyses of the computed difference scores demonstrated that the subject group with major depression had significantly less diurnal variation of Leu-11 NK cell levels (+1%) than the group of normal comparison subjects (–14%) between 8:00 a.m. and 4:00 p.m. (F=3.94, df=1, 44, p=0.05). The mean level of Leu-11 cells (percentage of lymphocytes, $10^6$ cells/ml) decreased from 12.6 (SD=5.9) to 11.0 (SD=4.9) between 8:00 a.m. and 4:00 p.m. for the normal comparison subjects. For the patients with major depression the mean Leu-11 levels were 10.6 (SD=5.9) at 8:00 a.m. and 10.8 (SD=5.4) at 4:00 p.m. The diurnal variation in mean NK cytotoxic activity was also found to be significantly less for the subjects with major depression (–24%) than for the normal comparison subjects (–45%) (F=6.72, df=1, 25, p=0.02). In addition, these differences were significant for each of the five effector/target cell ratios tested—200:1 (F=5.99, df=1, 25, p=0.02), 100:1 (F=4.94, df=1, 25, p=0.04), 50:1 (F=5.71, df=1, 25, p=0.02), 25:1 (F=4.47, df=1, 25, p=0.04), and 12.5:1 (F=5.64, df=1, 25, p=0.03)—and for the NK area under the curve (F=6.67, df=1, 25, p=0.02). The mean NK activity decreased from 44 (SD=13) to 24 (SD=12) between 8:00 a.m. and 4:00 p.m. for the normal comparison subjects and from 38 (SD=13) to 29 (SD=8) for the subjects with major depression.

The levels of Leu-7 cells did not differ significantly between the subject groups (F=2.58, df=1, 43, p=0.12). Partial correlations examining the relationship between Hamilton depression score and diurnal variation in the three immune measures were not significant. There were no significant depression-related gender differences in the diurnal variation of these immune measures.

## DISCUSSION

The results reported here indicate that the diurnal variation in NK activity is abnormal in patients with the syndrome of major depression. Normal circadian variation in NK cytotoxic activity varies as a function of changes in both the level of peripheral blood NK cells and the activation state of those cells over time (8). The Leu-11 antigen marker is present on virtually all cells in the peripheral blood that are known to have functionally meaningful NK activity, and peripheral blood Leu-11 NK cell levels are positively correlated with NK activity in normal subjects (5). As expected, the normal comparison subjects in this study exhibited substantial diurnal variation in circulating Leu-11 NK cell levels that tracked the diurnal variation of NK activity. In contrast, the patients with major depression had significantly less diurnal change in NK activity and almost no variation in Leu-11 NK cell levels.

Peripheral blood NK cell phenotype levels are thought to reflect lymphocyte migration or recirculation between immune organs (e.g., spleen) and blood. In healthy subjects the response of peripheral blood NK cells to stimulatory and inhibitory immunoregulatory signals appears to differentially vary during the circadian cycle (8). Hence, our finding that there is greater diurnal variation in NK activity than in Leu-11 NK cell levels among normal subjects is in keeping with evidence in the immunological literature which suggests that the daily bioperiodicity of NK activity is a function of changes in both blood levels of NK cells and the activation state of those cells. Given the finding that diurnal variation between 8:00 a.m. and 4:00 p.m. for both Leu-11 NK cell levels and NK activity is abnormal in patients with major depression, it will be important in future studies to examine multiple time points (e.g., every 3 hours) so that time series analyses can be used to systematically assess chronobiological differences (e.g., phase differences) throughout the full circadian cycle. Moreover, determining the dynamic temporal relationship between NK measures and neuromodulators that have been suggested to play a role in NK cell regulation (e.g., corticotropin-releasing factor, cortisol, β endorphin) will be important in testing hypotheses about their role in NK cell bioperiodicity.

Diurnal variation in Leu-7 lymphocyte levels did not differ significantly between the groups in our study, possibly because the periodicities of subgroups of Leu-7 positive cells are affected differently in major depression. Unlike the lymphocytes of the Leu-11 NK cell phenotype, Leu-7 antigens are found on a variable percentage (approximately 50%) of functionally active NK cells, as well as on subsets of T lymphocytes, some of which have patterns of rhythmic variation that differ from that of NK cells.

The clinical implications of biological rhythms have been of great interest to clinical researchers in psychiatry and other areas of medicine. Experimental evidence indicates that susceptibility to microbial infection, allograft rejection, and tumor growth, as well as immunopharmacologic responses, among other clinically relevant end points, vary significantly throughout the circadian cycle (9). One clinical study (10) indicated that asymptomatic HIV-infected individuals may manifest disruptions of the normal circadian cycle of CD4 (T helper) cells and that such disruptions may predate both symptoms of HIV-spectrum disease and, in some cases, reductions in CD4 cell counts. Since HIV infection affects the CNS as well as the immune system, it is possible that abnormal CD4 circadian rhythms may be secondary to chronobiological changes in the CNS.

In conclusion, by demonstrating that the normal diurnal variations in both circulating levels of the Leu-11 NK cells and NK activity are disrupted in patients with major depression, these data provide the first evidence that measures of immunological, as well as neural and endocrine, diurnal variation are abnormal in depression. Systematic investigation of interactions between complex neural, endocrine, and immune chronobiological rhythms may lead to greater basic understanding of the biology of brain-immune interactions in depression and perhaps other neuropsychiatric syndromes.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

### PSYCHOANALYSIS

**Other Times, Other Realities: Toward a Theory of Psychoanalytic Treatment,** *by Arnold H. Modell, M.D. Cambridge, Mass., Harvard University Press, 1990, 180 pp., $27.50.*

In retrospect, I find it interesting and no accident that I chose to read a book with this title while exploring aboriginal culture in the Australian outback. It was scarcely 90 years ago that white men entered and forever altered the aboriginal world. Can even the oldest aborigine be expected to remember what it was like before then, and, regardless, how could we assess that? About the same time, Freud forever altered the world for many of the rest of us, but Freud, like the rest of us, could not fully address everything he observed. Modell picks up on several of the pearls Freud uncovered but did not harvest or string together with his other ideas.

One of these unstrung pearls is the concept of *Nachträglichkeit,* which refers to the idea that memories are cyclically retranscribed over time into new cognitive and affective categories based on later life experiences. This concept produces a derivative theory that psychological development occurs in a cyclic, ongoing manner rather than in a linear, fixed fashion. Modell believes a reason this concept has not been explored in much detail previously is that Strachey mistranslated *Nachträglichkeit* as "deferred action," leading to a semantic self-fulfilling prophecy. Thus, *Nachträglichkeit* is basically a new and revolutionary concept for psychoanalysis, but it was used by Nobel Laureate (in immunology) Gerald Edelman in his 1987 book, *Neural Darwinism* (1). Edelman shifted his focus from the immune system's "memory" to the brain's memory functions. Edelman believes that memories are not simply laid down for life but are continually recategorized; retrospective attribution to past events occurs on the basis of subsequent psychic experiences. Thus, memories are reworked in a cyclic manner over time, so childhood emotional trauma or deprivation alone may not lead to later neurosis or other emotional disorders in a linear, predictable manner. Just as ontogeny does not recapitulate phylogeny, adult life is not necessarily just "new verses of the songs learned at mother's knee."

The concept of *Nachträglichkeit* is also captured in a paraphrase of Mark Twain: "When I was 15 years old, I thought my father was among the stupidest men on earth, and when I was 22, I was amazed at how much any man could learn in 7 years." Likewise, it is not possible for former analysands to fully perceive and describe how they have changed due to analysis; instead, they often think that the analyst or others have changed remarkably during the process.

Anna O. provided an anlage of this concept when she discovered that her severe hysterical symptoms could be lessened by self-treatment consisting of talking about upsetting thoughts and memories. In describing this to her physician, Josef Breuer, she coined the term "the talking cure" and the much livelier and more intriguing term "chimney sweeping." Her verbal catharsis removed the toxic accumulated residues of the emotional "fires" of her life. St. Augustine also recognized an aspect of *Nachträglichkeit* when he said there are three times: a present sense of things past, a present sense of things present, and a present sense of things future (p. 77).

Modell's central thesis in this book is that psychoanalysis works by leading to a reworking and recategorization of the patient's memories as well as by facilitating new experiences and perceptions based on the analyst's world view and on views creatively generated in the analytic setting. Based on that thesis, Modell redefines the ego as a mental structure engaged in processing or reorganizing (recontextualizing) our experiences through time. This thesis challenges a pillar of Kleinian analysis, namely, the primacy of the earliest experiences in determining later psychological life.

There are two secondary themes in the book. First, multiple levels of reality are present in the analytic setting, and those who cannot or will not learn to shift between the multiple levels of reality to understand the influences of these levels on their thoughts, feelings, and behaviors will not be able to achieve the highest level of psychoanalysis. Second, paradox is a part of mental functioning, especially of creativity; therefore, an appreciation and understanding of paradoxes will be part of the highest level of analysis. Modell's notion of "the paradox of time, that the past can alter the present and the present can alter the past" (p. 128) is implicit in Freud's ideas relating to *Nachträglichkeit.* There are other paradoxes in analysis: transference feelings are at the same time real and unreal, transference neurosis is partly a recreation of the past and at the same time a newly created illness, "transference is a major resistance to recovery and at the same time the motor that generates the cure" (p. 128), and the analyst simultaneously "represents the dangers of the past as well as the safety of the present" (p. 137).

Modell seems to blame Freud somewhat for not finding the concept of *Nachträglichkeit* as interesting and important as he has found it to be. A number of scientific advances in the past century, however, probably especially in the philosophies of science and linguistics, have made the concept more interesting and central than it may have seemed almost a century ago. In discussing Clover's 1931 paper, "The Therapeutic Effect of Inexact Interpretation," Modell implies that Clover would relentlessly pursue each fantasy in an analysis to the point of unattainable puritanical perfectionism before offering an interpretation (p. 93). I believe Clover's major intent was to suggest that we analysts listen beyond the first or second possible interpretation that occurs to us because wild analysis and shooting from the hip will otherwise increase the patient's resistance and defensiveness.

I found only two typos. On page 92, line 29, "than" should have been "then," and on page 123, a sentence reads, "I believe that in some instances the analyst's growing impatience with the analysand is ready to move to such a higher level of relatedness." I believe the phrase "indicates that the analysand" should follow "with the analysand" in the sentence.

Modell's ideas fit with my analytic experiences and are useful theoretically and therapeutically. A particular gem begins on page 119, where Modell gives a brilliantly concise integration of Kohut's concept of self-object with other psychoanalytic theories. This book should be read by psychoanalysts and psychoanalytically oriented psychotherapists, and teachers in these areas should incorporate it into the required reading for advanced psychiatry residents and psychoanalytic candidates. Like *Don Quixote,* it should be periodically reread, which further proves its central thesis.

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**Essential Papers on Transference,** *edited by Aaron H. Esman, M.D. New York, New York University Press, 1990, 528 pp., $55.00; $25.00 (paper).*

This ninth book in the Essential Papers series is an admirable and useful addition to the list. Dr. Esman chose 29 works, arranged in nearly chronological order, beginning with papers by Ferenczi and Freud in the early years of this century and ending with more recent articles by Kernberg and Cooper. Transference, despite its universality as a phenomenon, is of special relevance to psychoanalysis from a clinical standpoint. The material for this book, not surprisingly, comes entirely from the analytic literature.

Dr. Esman offers us, in the first 13 pages, his own thoughtful and well-written review of the 29 chapters. These he organizes into three "periods:" the pioneers (1909–1936), the middle (1936–1960), and the modern (1960–1987).

Freud regarded transferences as "new editions" of fantasies and feelings reawakened in the course of the analysis and transferred onto the person of the analyst. Toward the end of the pioneer period, Strachey claimed that successful analytic therapy depended on "mutative" interpretations that were "emotionally immediate." This immediacy could come only from transference interpretations. Esman notes that "reverberations of this shot are still being heard today."

During the middle period, controversy centered around the reliance on transference interpretation. Greenacre took a conservative stand, arguing for exclusive reliance on transference work. Greenson advocated a stance that allowed for more "realistic" gratifications and for less austerity, should the clinical situation warrant them. The personal attributes of the analyst, which tended to be ignored by the early writers, were shown to have important effects, especially when dealing with more fragile patients. The papers of Bibring-Lehner and Rioch address this topic.

The authors of the modern period make clear that, in analysis of the transference, one is not necessarily recreating the patient's actual past so much as the patient's emotionally valid past as remembered and reconstructed. The papers of Schafer, Kernberg, and Cooper are especially illuminating. The "modernist" model, as Cooper calls it, posits that transference is a new experience rather than merely a reenactment of an old one.

As every editor of a volume of Essential Papers is aware, some readers will take umbrage with the selection: omissions they feel should have been included and vice versa. In my own view, Dr. Esman has chosen well in 28 of the 29 papers, a highly respectable average. I would quarrel only with the Lacan paper, which is barely about transference and surely not "essential." This quibble aside, Esman's book is an excellent addition to the series and will be of great value to psychotherapists interested in the evolution and current applications of the concept of transference—so important in their work with patients.

MICHAEL H. STONE, M.D.
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**Collaborative Psychoanalysis: Anxiety, Depression, Dreams, and Personality Change,** *by Walter Bonime, M.D. Cranbury, N.J., Fairleigh Dickinson University Press, 1989, 394 pp., $55.00.*

This book is an accumulation of more than 35 articles from Walter Bonime's 33 years of psychoanalytic writing. He was one of the first students in Karen Horney's American Institute for Psychoanalysis. Dr. Bonime's work has continued Horney's focus on the social and cultural aspects of the psychoanalytic process. This text is not a dry series of old papers but a rich, refreshing view of many clinical situations. It touches many differing diagnostic issues in somewhat unique ways. For example, the section on depression and paranoia reflects Dr. Bonime's view that "depression is not a passively experienced or reactive interpersonal response, but an active means of relating to people." He sees depression as one of several problems that are the result of distorted adaptive styles of relating to people and points to the similarities among narcissistic, depressive, and paranoid processes. Dr. Bonime sees a similar origin of pathology in deficiencies in childhood social interpersonal experiences, and he highlights the anger, grandiosity, and "unwillingness to enhance the lives of others" of depressed individuals as well as their tendency to manipulate others while being "allergic to coercion" themselves.

An overall focus of the book is on how a person changes his or her "sense of self" during the psychoanalytic process. Dr. Bonime addresses the stages in a change in the sense of self and how this change is both resisted and facilitated in the collaborative effort of psychoanalysis. The book shows that over the years Dr. Bonime has thoughtfully treated and skillfully written about many aspects of human mental suffering. He has examined, in his own unique way, such areas as anxiety as a barrier to treatment progress, depersonalization as reflecting evolving health, homosexuality, marital conflict, and masturbatory fantasies.

Following up on his 1962 book *The Clinical Use of Dreams* (1), which was written with his wife, Florence, Dr. Bonime has included a rich section in this text on the role and use of dreams in psychoanalysis. His "culturalist" conviction that personality evolves through and is modified by interpersonal experience is reflected in his approach to dreams. He sees the dream as a frequently useful tool to help engage patients in learning about their unconscious emotional life. These papers include ideas such as the limitations of dream work in psychoanalysis and the use of dreams in brief focused psychotherapy. This section on dreams underscores the main theme of Bonime's work, which is to promote a better understanding of the collaborative effort of analyst and patient, working together to foster growth and constructive change.

Throughout the book we see the author's view of the origin of psychopathology and his multidimensional understanding of both the source of problems and the psychoanalytic process of change. He sees the cultural encouragement of competitiveness and cynicism as an important factor in causing personality distortions, and he shows how family cooperativeness is a source of emotional health. He gives straightforward views on such sticky issues as liking and disliking our patients. Another stimulating essay in this book concerns the process of psychoanalytic writing and the attempt to communicate with colleagues. He aptly relates our problem of attempting to translate "felt experience" of real interactions into abstractions that can both condense and communicate the material. Here again I found his examples and formulations very helpful.

Psychiatrists who spend some time reading these papers by Walter Bonime will be well rewarded and will appreciate his clarity and openness. They will gain from his broad clinical experience and his unique approach to many problems that we all experience in our efforts to help people with their emotional problems.

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**Psychoanalytic Terms and Concepts,** *edited by Burness E. Moore, M.D., and Bernard D. Fine, M.D. New Haven, Conn., Yale University Press, 1990, 210 pp., $35.00.*

The misuse of psychiatric and psychological nomenclature appears to be widespread (1). Psychoanalytic terms seem to be abused with particular frequency and, disturbingly, often by mental health professionals. Gabbard (2) pointed out the common overuse and misuse of the term "splitting." O'Boyle and White (3) noted the habitual use of the term "acting out," which has a precise psychoanalytic meaning, to refer to "virtually any misbehavior exhibited by children or adolescents." As a final example, I have observed many nonanalytically oriented psychiatrists and psychologists, who publicly eschew psychoanalytic thought, inappropriately use the term "countertransference" to refer to any emotional reaction therapists have toward patients.

In the light of all this, a book that offers well-written definitions and explanations of psychoanalytic terms is welcome. *Psychoanalytic Terms and Concepts* is such a volume. It contains lucid explanations of psychoanalytic terms as well as caveats about their frequent misuse, but this book is far more than a glossary. Most entries contain information on the development of the term, alternative usages, and cross-references to related terms. Additionally, the text is well referenced. Virtually every entry contains several key citations. The importance of this cannot be underestimated because even the best brief explanation of an abstract concept is necessarily limited. The inclusion of key citations enables serious scholars to obtain more detailed information.

There are also some mentions of alternative theoretical positions from research areas outside the strict psychoanalytic realm. For example, the entry on anorexia nervosa states that "various medical and sociological factors, including the widespread fear of being fat, seem to play a part in the increased incidence of cases." Thus, true to Freud's original formulations, it is recognized that hypothesized psychodynamic factors operate within broader biological and cultural contexts. To their credit, the editors have ensured that some entries note the extent to which theoretical hypotheses are supported by empirical data. Although this area could probably be improved by more extensive and frequent statements, such a change would necessitate changing an essentially well-annotated dictionary into an encyclopedia.

Finally, in this age of reference tomes costing more than $100.00, this brief but still comprehensive source is modestly priced. In short, there is much to recommend this volume to students, teachers, clinicians, and scientists.

The goals of science are generally taken to be the prediction, explanation, and control of natural phenomena. Each of these is predicated on the precise description of these phenomena through a shared language. Freud stated that "even in its caprices the usage of language remains true to some kind of reality" (4, p. 111). *Psychoanalytic Terms and Concepts* may help our use of psychoanalytic language to be a little less capricious and a little more true.

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**Dimensions of Psychoanalysis,** *edited by Joseph Sandler. Madison, Conn., International Universities Press, 1990, 263 pp., $35.00.*

University College, the oldest of the colleges of the University of London, instituted a visiting Freud Memorial Chair in 1974. Holders of the 1-year professorship traditionally gave an inaugural lecture, and this volume contains those given until the chair was converted to a 5-year position in 1984. Joseph Sandler, the first long-term holder of the Freud Memorial Chair, is the editor of these 12 papers by 11 internationally recognized psychoanalytic scholars. Having also been an earlier 1-year professor, Sandler contributes two papers as well as an introduction. Most contributors are clinical analysts. The lectures include American, British, and French views. As could be expected, all of the papers are excellent.

Sandler claims that the lectures demonstrate how much and how fruitfully psychoanalysis has developed since Freud's death. He is correct, of course, and that makes this book of particular value to those psychiatrists who have not kept current with psychoanalytic ideas over the past decade and a half. I refer not only to progress within the Freudian tradition but also to the greater acceptance of clinical theory based on the contributions of Melanie Klein. This development is represented in the volume by both Hanna Segal's lecture and Sandler's own recognition of the increased interaction between the Freudian and Kleinian points of view. His position is that there is no necessary incompatibility between a psychology based on unconscious wishes and an object relations psychology.

Although the lectures cover vastly different topics, themes recur. The importance of the real world as well as the private, personal, internal world of fantasy and affect appears in work as far apart as that of John Bowlby on attachment and separation, Christopher Lasch on "The Freudian Left," and Janine Chasseguet-Smirgel on perversion. The importance of the preoedipal phases of development and the question of whether psychoanalysis is a science or an art reverberate through several papers.

Roy Schafer's chapter introduces his now well-known view that psychoanalysis needs a new language to replace Freud's metapsychology, a language based on a conception of personal existence as actions with multiple and transformable meanings. William Gillespie deals with basic Freudian ideas and does this briefly, clearly, and well. Hanna Segal uses case material to illustrate the developmental progression from split-off omnipotent fantasy to thought and the freedom that this engenders. Sandler notes that it is untenable to derive all unconscious wishes from sexual and aggressive impulses—that wishes to restore the feeling of security or self-esteem or well-being or a lost object are of equal significance. Andre Green proposes a category of tertiary thought process—beyond Freud's primary and secondary processes. He then goes on to discuss patients for whom the love of others is always uncertain but hatred is always sure—for whom fixations on hatred are much more tenacious than fixations on love.

Bowlby's chapter succinctly summarizes the source and product of his own work on attachment, separation, and loss. Christopher Lasch describes why psychoanalysis has more to say on the psychology of power than any other theory of the mind and why this appealed to elements of the political left. Karl Pribram argues that psychoanalysis would suffer a substantial loss if it abandoned its energy concept in favor of modern formation-process ideas. He reviews the experimental analysis of the neural mechanisms involved in motivation and emotion and claims that such work clearly argues for the primary transformations of energy in the behavioral economy of living systems. John Klauber's paper takes up the role of illusion in psychoanalytic treatment—by which he means the nature and value of surrender to the transference induced by psychoanalysis. Chasseguet-Smirgel presents her view that perverse temptation leads to the acceptance of pregenital desire and satisfaction as equal or superior to genital desire and satisfaction because such an objective erodes the differences between the sexes and the generations. In her view, perversion is an attempt to free oneself from a paternal universe and the law.

Albert J. Solnit's lecture deals with preparing a child for potentially traumatic experience so that remembering can contribute to development rather than impair it. Solnit's case material is particularly illuminating as well as affectively moving. Sandler's concluding chapter asks whether the concept of the child within the adult may not be a better way for the clinician to help the patient become friends with the previously unacceptable parts of himself than the concept of id.

As a collection, these papers make me a bit sad that the inaugural lectures of the Freud Memorial Chair are no longer an annual event.

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## PSYCHOANALYTIC CONTROVERSY

**Melanie Klein, vol. I: First Discoveries and First System 1919–1932,** *by Jean-Michel Petot; translated by Christine Trollope. Madison, Conn., International Universities Press, 1990, 313 pp., $40.00.*

Melanie Klein represents a historically important extension of psychoanalytic thought. During her lifetime (1882–1960) she established her own school in Great Britain, which has continued to be influential there and has subsequently had a notable impact on Latin America and now elsewhere as well. When she first started developing her theories, Freud saw her work as a challenge to himself that took the form of an attack on the efforts in child analysis of his daughter Anna. As the years passed, Klein developed her ideas into what she considered a "system." She took a different approach, for example, to the psychology of women, she worked with play as a technique for treating children, and she sought to link normal development much more closely to psychotic problems than so-called classical psychoanalytic theory has ever accepted.

A fierce debate over Kleinianism raged within the British Psycho-Analytical Society toward the end of World War II. Klein and her supporters not only succeeded in not getting repudiated as "heretics" but, in the end, it was Anna Freud who felt obliged to resign from a post in the British Society in order to spend her efforts at her own child therapy clinic in Hampstead. Although the British Society remained formally united, two separate training streams were set up within it so that Anna Freud's students would not have to be involved with the concepts that Klein cherished.

*Melanie Klein, vol. I* is a curious book. Perhaps the single most notable point to comment on is that it first appeared in France in 1979. Since this text covers Klein's work only in its first phase I am reluctant to generalize about all Petot has to say, but there is enough here to be disquieting, not just about the nature of Kleinianism but about the state of publishing in the United States and the history of psychoanalysis here as well.

I cannot understand how the publisher could allow this 1979 book to appear in translation without any attempt to bring the material up-to-date. A lot of historical research has appeared over the last decade, and it seems irresponsible to allow an old text to come out without a new introduction, by the author or someone else, trying to incorporate recent research into the story as originally reconstructed in 1979.

Furthermore, Petot seems to have an inadequate amount of distance toward Klein's theories. We are told, for instance, that the child patient in an early 1921 paper of Klein's was really her youngest son. I am troubled by the fact that Petot makes no effort to come to terms with the moral propriety of Klein's having treated her son. Furthermore, it is now evident, although Petot did not know it in 1979, that Klein analyzed her two other children as well and put them into her writings as disguised clinical cases.

Even more fundamentally, I would question the correctness of describing Klein's writings as in any sense "discoveries," as proclaimed in the subtitle to this book. As far as I am concerned, Freud himself contributed a critical new way of looking at things; to call his concepts, or those of any of his followers, "discoveries" has to imply a degree of scientific standing that is belied by the very nature of the kind of unreconstructed text that *Melanie Klein, vol. I* constitutes.

Science entails change and fresh developments, as well as the possibility of confirmation. The fact that the publisher felt free to bring out a 1979 text without revising it in the light of new knowledge indicates something of the nature of the essentially religious side of what has happened to all too much psychoanalytic literature.

Those outside psychoanalysis have long bewailed the absence of genuine research in this field, and the publication of this book only confirms the worst that critics have thought Freudians have been up to. Melanie Klein herself not only lacked medical training but never attained any kind of higher education; her ideas might of course be sound nevertheless, but it is striking that she proposed that the psychoanalyst's task was to "cure" all children of their so-called psychoses, an enterprise that I myself have to regard as a menacing kind of proposed enterprise.

General readers deserve help in trying to understand Klein's work, even if they cannot swallow the idea that she succeeded in creating a theoretical structure which deserves to be analyzed and interpreted as if it were a developing holy writ. Petot's book is not reliable as history. If readers want to look at an interesting account of another early child analyst, I can highly recommend *Hermine Hug-Hellmuth: Her Life and Work* (1).

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**The Freud-Klein Controversies: 1941–1945,** *edited by Pearl King and Riccardo Steiner. New York, Tavistock, 1991, 958 pp., $175.00.*

Unfortunately, the outrageous price of this book will preclude its receiving the widespread attention and readership that it deserves. The controversial problems that were introduced into psychoanalysis by Melanie Klein reached a crisis situation in the British Psycho-Analytical Society shortly after Freud's death in 1939. This produced a series of "extraordinary business meetings" and "scientific controversies" in the Society, and the book under review contains the minutes of these meetings and the papers and discussions presented in the scientific controversies, without slant or partisan remarks by the editors (who do, however, add some clearly marked and helpful "editorial comments"). As such, it represents an extremely valuable contribution to the history of ideas and the history of psychoanalysis.

Even more valuable are the descriptions of the incredibly personal narcissistic and other investments that are demonstrated here as underlying apparent "scientific disagreements" in the field. Stein (1) recently pointed out that countertransference has a hitherto unrecognized important further source, "deriving from the utilized theory of the analyst. This countertransference may occur independently of the patient's motivation and independently of the internal dynamics of the analyst." The powerful investments in various theories and the personal rancor with which they are debated are better illustrated in *The Freud-Klein Controversies* the volume under review here than in any other long volume in the field to my knowledge.

The reader should keep in mind that the background of these controversies is World War II in England, including the London "blitz" during which some analysts left the city and others intrepidly carried on what functions were possible. This was complicated by the influx of refugee psychoanalysts from Europe, including the Freuds themselves, and the inevitable chaos, competition, and confusion that such an influx as well as the horror of prolonged bombing and the deprivations of war always bring. Even more painful is the fact that the most outspoken and vitriolic attacker of Melanie Klein and the Kleinians who followed her was Melitta Schmideberg, Melanie Klein's daughter. In a way, it is to the credit of British civility that the matter became resolved without an actual fragmentation of the British Psycho-Analytical Society. King tells us,

> Overtly, controversy was mainly couched in terms of scientific differences of opinion about what was considered to be accepted psychoanalytical theory and technique, as formulated by Freud, and what view of it should be taught to students of psychoanalysis or included in public lectures by analysts representing the Society. Inevitably, these issues also masked deeper ones to do with who should decide these questions, and therefore, which individuals and groups held power in the Society. (p. 9)

Klein's work caused controversy in the Society because she treated children's play as if it were the equivalent of an adult patient's free associations and because she interpreted negative material and aggressive impulses of adult patients when they appeared "without the customary nurturing of the positive affects of the patient, without which it was widely held in the Berlin Society that psychoanalysis could not proceed" (pp. 18–19). This controversy continues today in the arguments between the followers of Kernberg and the followers of Kohut (2). The British Society debate was between the followers of Klein and the followers of Anna Freud, who held that it was important to foster a positive response from the child and that a transference could not develop in child analysis because the affects of the child were still tied to their parents. So Anna Freud's approach was more educative and explanatory than interpretive. Klein's critics also objected, as they do today, to her emphasis on fantasy to the neglect of environmental factors, her interpretation of Freud's concept of the death instinct, her early dating of the development of the superego, and her confusing concept of "internal objects." As anyone who has attempted to teach Melanie Klein's views to residents in psychiatry will attest, they are among the most difficult to accept at face value and seem to the residents as they did to Walter Schmideberg, who tells us in the book under review,

> Papers became more and more confused as the years went by. I listened to them in silence and some of them made me think that the accusation of our enemies that it is impossible to distinguish between the phantasies of the patients and those of the analyst contained more than a grain of truth. Reality seemed to disappear or become distorted. Everything was internalized and still more internalized. I sometimes thought I was following Alice through the looking glass and even seemed to hear the voice of the Mad Hatter. (p. 86)

Still, as Holland (3) has pointed out, fundamental insights can emerge from such controversial discussions, and the most important part of the book for those immersed in the clinical practice of psychotherapy or psychoanalysis contains the reports of the scientific discussions themselves. As Steiner (4) noted, there is also much to be learned from an examination of the power struggles and narcissistic investments demonstrated in the Freud-Klein controversies for those who are involved in the current power structures and hierarchies of organized psychiatry and psychoanalysis.

For the ordinary working clinician the crucial issue is to what extent the Kleinian point of view has validity and usefulness in everyday practice. Here the central part of the book (sections two, three, and four) is most valuable and requires careful study. I wish the publisher would produce selections from this central part in an inexpensive paperback because it would be a great act of kindness to students who must study this material but cannot afford $175.00 for one book.

There is no space in a review to outline in any greater detail the opposing scientific points of view that are covered in this book (Anna Freud does this beautifully on pages 417–425) as well as some of the problems described that seem to occur inevitably in the system of psychoanalytic training carried out by training analysts—problems of identification, indoctrination, and the continued relationship of training analysts and candidates after the cessation of the so-called training analysis.

These problems, of course, have been recognized elsewhere; they reached their peak of scandalous proportions in the dramatic vicissitudes of Jacques Lacan and his ever-changing schools and alliances during his meteoric career in France.

It is important to note that "unconscious phantasy" is deliberately spelled with a "ph" throughout the book in order to differentiate it from conscious "fantasy," as explained on page 242. This distinction has largely dropped out of the current literature. This is no minor issue, since one of the most caustic debates rests on the fact that Anna Freud and her colleagues could not accept the notion of "unconscious phantasy" as central to the first months of the life of the baby, especially the violently aggressive "phantasies" emphasized in Kleinian theory. The notion of "unconscious phantasy" became central in the controversies; Anna Freud's followers accused the Kleinians of an increasing mysticism based on it, and the Kleinians saw it as the key to more and more scientific discoveries and explanations of various forms of adult psychopathology. As Steiner explains here, "The notion of unconscious phantasy therefore became the theoretical rampart, the scientific paradigm, around which the Kleinians organized their defense and the weapon they used to lead their attacks" (p. 253).

The thrust of American psychiatry today seems to be away from the Kleinians in that more emphasis is placed on the actual environmental events that surrounded the child and infant than on the unconscious fantasy life that is so difficult to investigate and validate, but the matter is largely unsettled. It is extremely important to differentiate Klein's views from those of Anna Freud's traditional psychoanalysis. According to the Kleinians, "phantasy is the mental corollary, the psychic representative of instinct" (p. 277), but in the traditional view unconscious fantasies are already compromise formations in the Freudian drive/conflict/anxiety/defense/compromise sequence. Of course, for the Kleinians fantasy can also be a means of defense against anxiety, but their notion, as the fiery Glover points out (pp. 397–400), is far more basic, developmentally earlier, and all-encompassing than Freud's "hallucinatory wish fulfillment" because, for them, "phantasy expresses the specific content of the urge (or the feeling, e.g., hate, anxiety, fear, love, or sorrow) which is dominating the child's mind at the moment" (p. 277). This leads to the Kleinian claim that "fantasy is the primary content of all mental processes" (pp. 276, 334). It is hard to imagine how this could be verified.

I highly recommend this wonderful book for advanced students in the field of psychiatry, especially those who are interested in doing psychotherapy or psychoanalysis, those who are interested in rising in the power hierarchy of organized psychiatry and psychoanalysis, and those who are involved in a study of groups or group processes.

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The Prisonhouse of Psychoanalysis, *by Arnold Goldberg. Hillsdale, N.J., Analytic Press, 1990, 175 pp., $26.95.*

The intriguing title of this book refers to the constraints of psychoanalysis. Goldberg appreciates that every discipline has its limitations, whether imposed by the dominant paradigm, simple ignorance, the priorities of education, publication, and funding, or, more insidiously, by pressure for conformity that usually accompanies acceptance into the select inner circle, i.e., those certified by a Ph.D. or M.D. membership in the American Psychoanalytic Association, etc. Psychoanalysis, with its dependence on N=1 research studies, the requirement of a long personal treatment in which one's personality is analyzed, and its tendency toward the deification of important contributors, may be particularly prone to all these constraints. This is not to argue that constraints are a necessary—or unnecessary—evil. They can also be a source of discipline and modesty and a stimulus for creative endeavor. Goldberg's concern is that in psychoanalysis the constraints have become subversive and the existing discipline of psychoanalysis has become a prison house as a result. The author is a widely read and highly esteemed psychoanalyst whose credentials are excellent. He speaks as both an "insider," having successfully mastered traditional analysis, and an "outsider," a leading proponent and co-creator of the self psychology of Heinz Kohut, which has been one of the major efforts in the last two decades to revise traditional psychoanalysis.

The book is far-ranging. The first chapter discusses the deterioration of psychoanalytic practice into meaningless clichés. Psychotherapists, particularly inexperienced ones, will enjoy Goldberg's discussion of such issues as abstinence, honesty, and attentiveness in therapy. Later chapters are more original. His comparison of addiction, hero worship, and the rigid codification of rules in psychoanalysis as a means of overcoming personal loneliness and providing insulation against uncertainty is interesting. The most original aspect of the book is his discussion of the role of internal representations in the mind and how they relate to treatment. Goldberg compares Freud's notion of an inner world distorted by conflict and desire, Lacan's inner world of unending unsatisfying signifiers, and Kohut's rejection of any theory of the inner world as incomplete and needing the external world to complete it. Freud and Lacan have "storehouse" theories, whereas Kohut's theory is a "connection" theory. The connection between self and object, the famous self-object theory of Kohut, is well elaborated. Goldberg attempts to define it and distinguish it from a theory of object relations and interpersonal theory.

Goldberg has a knack for discussing psychoanalytic issues within a larger context of philosophy, linguistics, literature, and science. He is at his most eloquent in proposing that the principal prison house of psychoanalysis is its imprisonment of practitioners within an incorrect theory of mind. "We are locked within a boundary wall and are so separated from each other and other ideas. We must recognize our coupling with others" (p. 128). He can also become passionately philosophical. In his chapter on the self in psychoanalysis and the importance of self-objects he writes, "The process is one of discerning the nature of those group and cultural selfobjects which encourage development, which promote a being-in-the-world that does away with the isolated individual in a sea of separate objects, and which is liberated from the prevailing sense of survival that so sadly dominates our psychoanalytic thinkers."

The book might have benefited from better editing. What seems to be petty swatting at people who have injured Dr. Goldberg's feelings does not really contribute to the more original and important discussions in the later chapters. Also there is a tone of dogmatism about the book that might stimulate strong feelings rather than thoughtful discussion in some readers. In a story that is humorous but perhaps more cynical than intended, Dr. Goldberg reports how he and a colleague listened to the presentation of a third colleague. As Dr. Goldberg formulates his objections to the presentation he realizes that the colleague sitting next to him is doing the same thing and that each knows what the other is going to say. The speaker is described as taking a "rather one-sided and biased position." Goldberg makes no comment on what the presenter and the colleague next to him would say of his own position. We never find out. They leave the discussion to go for a cup of coffee. More of an "over a cup of coffee tone" would have helped the book.

Nevertheless, I recommend this book. It should be of interest to most readers of the *Journal* who are psychodynamically and/or psychoanalytically oriented and who would like to know what one worthy critic of much of this scene has to say.

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**The Freudians: A Comparative Perspective,** *by Edith Kurzweil. New Haven, Conn., Yale University Press, 1989, 362 pp., $35.00.*

Professor Edith Kurzweil, Chair of Sociology at Rutgers University and Executive Editor of *Partisan Review,* has performed an unexpected service for American psychiatry. Her book, which can be read on many different levels, will be invaluable and essential reading for all practicing clinicians, whatever their persuasion.

For the nonanalytically informed clinician the four chapters constituting part two, Applications of Psychoanalysis, locate the contribution of psychoanalytically informed thought to psychosomatic medicine, education, the psychology of women, literature, and criticism. The chapter on the psychology of women is invaluable in indicating how far psychoanalysis has moved from its initial promulgation of sexual stereotypes as "science" to an emerging tool for the critique of stereotypes. For the psychoanalytically sophisticated clinician, part one, Psychoanalysis Before 1945, is a superb cross-cultural history of the development and reception of Freud's theory in a variety of social contexts.

I would expect that all clinicians would benefit from reading part three, Psychoanalysis Since 1945. In particular, chapter 11, "Theoretical Innovations," is simply the best summary of the current state of psychoanalytic theory and technique. For example, when explicating the contributions of Otto Kernberg, Professor Kurzweil shows how psychoanalysis has not only enriched the cultural context with which it has come into contact but also been influenced and enriched by its contact with a variety of social contexts and influences. At the same time, her summary of Kernberg's work is simply the best brief introduction I know of.

Professor Kurzweil is such a capable synthesizer that I can only hope she will continue to pay attention to and report on new developments in psychoanalysis. For example, the influence of the pioneering work of Alan Stone, Professor of Law and Psychiatry at Harvard Law School, is seminal to our understanding a wide range of pressing medical, ethical, and legal issues. At the same time, attempts at integrating psychoanalytic innovations with neurobiological models, such as Arnold Modell's, show promise of bridging the gap between biological and psychological understanding of that improbable, wonderful work we call man. Professor Kurzweil's attention to context is most welcome, as these and other pioneering efforts proceed to bear both clinical and cultural fruit.

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## NEUROBIOLOGY

**Neurobiology of Stereotyped Behavior,** *edited by Steven J. Cooper and Colin T. Dourish. New York, Oxford University Press, 1990, 297 pp., $65.00.*

The broad title of this book is misleading and unfortunate. Once one gets over the disappointment over its relatively narrow focus, however, *Neurobiology of Stereotyped Behavior* is a useful update and review of neuropharmacological and behavioral understanding of stereotypy, primarily in rodents. Of the 20 contributors, half are from the United Kingdom, and almost all are basic scientists—neurochemists, pharmacologists, or experimental psychologists.

The editors provide a splendid introductory historical overview of the concept of stereotypy and the role of brain dopamine. For anyone graduating from medical school after 1960, this brings an important perspective as to the role of basic research on dopamine pathways and on psychostimulant-induced stereotypies in early formulations of schizophrenia. The recognition that dopamine is a major neurotransmitter in the normal mammalian brain, that brain amine metabolism is crucial for amphetamine-induced stereotypy, and that the location of CNS site is qualitatively important for stereotypies were seminal for an entire generation of psychiatric theories.

The greatly increased complexity of our understanding of the receptors mediating stereotypy is elaborated in a series of chapters on dopamine subtypes and stereotyped behaviors. For example, there are chapters on the role of $D_1$ receptors, the neural basis of drug-induced yawning (complex, catecholaminergic, serotonergic, and peptidergic) and the fascinating association between induction of yawning and of sexual excitation, neuropeptides and stereotypy in behavior, and stereotyped and other motor responses to 5-hydroxytryptamine (5-HT) receptor activation. All of these chapters provide lucid introductions that are useful to the experimental psychologists who may read the book as well as to the occasional clinician-researcher.

Researchers in obsessive-compulsive disorder will be particularly interested in the role of neuropeptides, particularly in grooming behaviors. The complex interplay between dopamine and ACTH-induced grooming (chapter five) as well as its role in 5-HT receptor activation is also provocative in the light of the increasingly complex psychopharmacology of compulsive rituals in obsessive-compulsive disorder.

There are also chapters on transmitters demonstrating different aspects of control of stereotyped or repetitive behaviors. These are less successful for the general reader, although the point is made that there are complex influences on the amount and type of stereotypies over and above drug dose and dopamine pathway. More general issues such as possible adaptive role of stereotypies, the question of a continuum of behavioral activation, and relevance for models of mental health are interesting, but the extensive microanalyses of behavior are not convincingly useful.

The explosion of research on compulsive ritualized behaviors makes this work of more topical relevance than it would first seem. For this reason, I recommend it to researchers in obsessive-compulsive disorder and the curious clinician occupied with mental retardation, obsessive-compulsive disorder, or any neuropsychiatric disorder with excessive repetitive behaviors.

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**An Introduction to Neurotransmission in Health and Disease,** *edited by P. Riederer, N. Kopp, and J. Pearlson. New York, Oxford University Press, 1990, 394 pp., $98.00.*

This book is quite a buffet with many courses, a gluttony of neurotransmitter science with a great variety of dishes. As the internal structure reveals, it is written in the European tradition of biochemical and pharmacological presentations. The book is divided into sections such as General Phenomena Involving Neurotransmission, Neuroendocrinology, Central and Peripheral Autonomic Nervous Systems, Locomotion, and Emotion, Pain and Addiction (which includes the psychiatric disorders). The final section, Higher Cerebral Function, deals with pediatric topics, ischemia, dementia, coma, and epilepsy. There are chapters on the anatomical distributions of the monoamines and peptides, amino acids, neurological and psychiatric diseases, the biochemical changes following coma and brain ischemia (which one day will lead to rational treatment of the damage of strokes and spinal cord trauma), memory, and developmental, degenerative, and acquired diseases of the autonomic nervous system such as the Shy-Drager syndrome, as well as pediatric disorders such as sudden infant death syndrome.

The excitement of the neurosciences is that different disciplines need each other to advance the field, each nibbling away on small pieces of the many puzzles that the brain poses. Psychiatric disorders have found a place in the neurosciences and may well have been the primary stimulus for studying the brain. This book is compiled by neuropathologists, neurochemists, and neurologists, with minimal input from psychiatrists as far as I can determine. Only a decade ago neurologists were grossly uninterested in neurotransmitters and their mechanisms in the brain or in the autonomic nervous system. It seems as if with this book the neurologists are reclaiming the neurosciences. We should not forget that Freud was first of all a neurologist who made his name in aphasias, then as a pharmacologist, and finally as a psychiatrist. Interestingly, reading this book, it seems as if the mental health neuroscientists have not been the major promoters of the neurotransmitter studies from the beginning. Schizophrenia, the most mysterious of the psychiatric disorders, as well as depression, anxiety, and alcoholism, are presented as mere syndromes by nonpsychiatrists.

Unfortunately, this book is a product of its grand design. Bringing so many scientists together in an integrated text is not a small accomplishment. It is even more difficult when editors and contributors come from the United States, France, Germany, England, Belgium, Hungary, Pakistan, and Japan. Not unexpectedly, this books suffers because the interval between writing and publishing was too long. As the editors point out, being out of date is certainly a risk of the fast-moving neuroscience literature. It may explain why many of the chapters do not have references beyond 1986, except for some updates. On the other hand, there is enough information to provide beginning students or scientists who are looking to branch out into new directions an adequate basis to build on.

In its concept the book is clearly a product of the mid-1980s. Indeed, it misses such recent exciting developments as diazepam binding inhibitor; dopamine $D_3$, $D_4$, or $D_5$ receptors; G proteins; neurosteroids; membrane phospholipids; brain autopsy studies of peptides in schizophrenia; the presumed mechanisms of cocaine addiction; and ethanol interaction with the chloride channel/$\gamma$-aminobutyric acid$_A$ receptor complex, but that is unavoidable. As Pearlson states in his introductory chapter, "It is fairly easy to begin analyzing the human nervous system and its diseases but impossible to finish" (p. 7). On the other hand, there is little conjecture; the basics are there.

Pearlson also notes that "in approaching the analysis of the brain and its diseases it is necessary to be cautious of dogma and open to heterodox; indeed the probing brain needs to be as intelligent and plastic as it is capable of being. Current efforts are imperfect but a considerable degree of success has been achieved" (p. 19). The editors of this book have done a service to the field to summarize disparate neuroscience phenomena, illnesses, behaviors, and physiological functions as they relate to neurotransmitter function and make them accessible. In the preface the editors state that the book is meant to be an introduction to students of the different disciplines that make up the field of neuroscience as well as for more established scientists to see their work in a broader context, in the hope that cross-fertilization may occur. Psychiatric and neurological residents could make good use of it as well. As the editors stress, the book may lead to collaborations. I enjoyed the book, discounting an occasional typo. The diagrams emphasized by the editors, although not present in all chapters, increase its readability. In a way it may belong to the classics of neurosciences such as *Psychopharmacology: The Third Generation of Progress* (1), *The Biochemical Basis of Behavior* (2), and *The Neurobiology of Spinal Fluid* (3, 4). It appears that the editors achieved what they set out to do. I will be looking forward to a second edition or an update in a few years.

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**Amino Acids in Psychiatric Disease,** *edited by Mary Ann Richardson, Ph.D. Washington, D.C., American Psychiatric Press, 1990, 190 pp., $22.50.*

This volume in the Progress in Psychiatry series reviews the roles of a number of precursor amino acids in psychiatric disease. Initially, the almost total absence of discussion regarding the neurotransmitter amino acids was disconcerting for a book with this title; perhaps adding a modifier (e.g., precursor, neutral, plasma, etc.) would more accurately reflect its content. The amino acids under discussion include tyrosine, L-tryptophan, and phenylalanine (precursors or modifiers of monoamine synthesis and function), not glutamate and $\gamma$-aminobutyric acid (GABA) (neurotransmitters). Despite the limited scope of the volume relative to its title, the topics covered are of great interest as applied to a wide range of psychiatric diseases. These are topics that were formerly at the heart of psychiatric neuroscience research, given its emphasis on the monoamine neurotransmitters dopamine, norepinephrine, and serotonin.

As other neurotransmitter systems involved in mental processes have gained in importance, the "traditional" amines have moved from center stage to part of the chorus. Unfortunately, as our scientific focus changes we sometimes forget the value of former approaches in our excitement over "new" findings. This volume nicely illustrates that exciting progress is still underway in an area of psychiatric neuroscience that was in vogue, then was eclipsed, but may be poised for a stimulating renaissance based on the work of the contributors to this volume. The theme of an abnormality in amino acid membrane transport manifesting as mental illness is recurrent throughout the book—seven of the nine chapters relate to this idea in considerable detail, and the other two mention the significance of such alterations.

The chapter by the editor on plasma phenylalanine and vulnerability to tardive dyskinesia presents an intriguing hypothesis regarding predisposition to tardive dyskinesia based on abnormal metabolism of this amino acid. The theory rests on the findings of greater-than-expected rates of tardive dyskinesia in individuals suffering from phenylketonuria and the finding of significant correlations between plasma phenylalanine and tardive dyskinesia. There has been a notable lack of progress in the identification of other pharmacological risk factors for tardive dyskinesia, and this approach may yield an explanation of why this has occurred. In a similar vein, the paper by Moller demonstrates how plasma amino acid ratios may predict antidepressant efficacy better than clinical or pharmacokinetic variables.

Given the known actions of antidepressants on monoaminergic systems it is quite reasonable that much effort would go into understanding the regulation of these neurotransmitters. This topic is covered very thoroughly. If anything, the discussion of catecholamine regulation by amino acids is somewhat redundant, especially in the light of the complete omission of any discussion of, for example, the role of GABA in anxiety disorders or benzodiazepine function. What is presented here is well thought out and thorough, but I hope the next edition will include specific discussions of the neurotransmitter amino acids with their implications for psychiatry, including anxiolytic function, regulation of neurotransmission, and the possible role of excitotoxicity in neurodegenerative disorders.

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**The Clinical Relevance of Kindling,** *edited by Tom G. Bolwig and Michael R. Trimble. New York, John Wiley & Sons, 1989, 312 pp., $67.50.*

In 1967 G.V. Goddard demonstrated that repeated administration of subconvulsive electrical stimulus to different areas in the brain (especially in the olfactory-limbic system) of laboratory animals could lead to the gradual development and intensification of behavioral convulsions. This "kindling" phenomenon occurs under explicit circumstances of intracerebral, spaced, discrete, repetitive subclinical stimulation in specific brain regions in sensitive individuals. The clinical effects of kindling are long-lasting, and permanent changes (reactive gliosis, for example) in the brain of kindled animals have been reported.

Although kindling in the strictest sense cannot intentionally be demonstrated in man, many researchers have been excited by the similarities between the phenomenon and certain clinical conditions. Not surprisingly, a kindling model for epilepsy, especially temporal lobe epilepsy, has been proposed. But there are also suggestions of connections between kindling and personality disorders, panic attacks, manic-depressive illness, schizophrenia, alcohol and cocaine withdrawal, and movement disorders. This seems a fairly large expectation for the explanatory power of the kindling model. In some instances, the authors use the term "kindling-like" phenomenon, preventing the reader from a too-close connection between kindling and psychopathology. In fact, most of the contributors clearly state the lack of evidence for a kindling model in any of the clinical conditions mentioned here. Consequently, they generally call for future research to clarify the field.

We are living in a time when psychopathology badly needs brain models to lean on. Links between basic neuroscience and clinical manifestations of brain disorder are to be welcomed. This book clearly demonstrates that the kindling model stands as one of the few and most interesting of such bridges in the field of neuropsychiatry. As one of the authors puts it, "The attempts to account for different clinical syndromes . . . by a kindling-like phenomenon certainly demonstrate some heuristic value of this concept in biological psychiatry. However, a claim for construct validity definitely awaits future animal and clinical studies."

This book, the result of a symposium that gathered the main specialists in the field, covers a wide range of topics relative to kindling. Clinical relationships occupy several chapters, but reviews of basic aspects of kindling, kindling and memory and learning, chemical kindling, and kindling and antiepileptic drugs are also included. Of special interest to the clinical psychiatrist is the chapter on kindling and ECT by M. Fink, who vigorously rejects the analogy between these two kinds of electrical brain stimulation. Not only psychiatrists but also neurologists, epileptologists, and neuroscientists will find interesting and useful insights and information in this book.

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## NEUROPSYCHOLOGY

**Clinical Neuropsychology and Brain Function: Research, Measurement, and Practice,** *edited by Thomas Boll and Brenda K. Bryant. Washington, D.C., American Psychological Association, 1988, 202 pp., $24.00.*

This short work is composed of lectures in neuropsychology from the American Psychological Association's 1987 annual meeting. Animal studies and human studies are covered.

Stein begins the book with a chapter that criticizes the functional localizationist paradigm. He offers an alternative, namely, that the context in which CNS trauma occurs may powerfully contribute to the severity of an injury. His own classic work has focused on the differential effects of serially staged compared with single-stage lesions. The sequelae of the former are less severe than those of the latter. This finding is of obvious clinical relevance. On the other hand, Stein's attempt to minimize the role of the hippocampal-amygdala system in memory is probably misguided, given the amount of convergent evidence from primates, penetrating head wounds, and dementia. One caveat is that Stein's chapter does not bear directly on the issue he first raises—the existence of discrete processing modules.

Thompson's lecture is conversational in tone and rich in detail. He has posited that the mossy-fiber granule-cell parallel-fiber system and the climbing fiber system are learning and teaching units in the rabbit cerebellum. He goes on to claim, with evidence to support his position, that memory trace circuits are localized. Thompson's work is internationally recognized. I only wish he had added a section on the theoretical distinction between the classical conditioning paradigms, including eye blink, thought to be "procedural," and declarative or representational memory, which might involve diencephalic and medial temporal lobe neural systems in humans.

Dennis presents a model for conceptualizing the effects of brain damage in children. In her ambitious effort to create such a framework, the actual data to support her ideas are shortchanged. After creating the framework, she presents complicated data in a clear and focused way. For instance, she shows how the systems that are involved in the development of an ability may be different from those which sustain the ability. Regarding her work on early left hemisphere injury in children, I wish she had addressed the work of Smith and Chadwick, who did not find marked language deficits after such insults in children. Dennis also presents evidence for the etiology and neuropathology of language disorders based on factor analysis and multiple regression. Despite the rarefaction of data imposed by her statistical techniques, her results and conclusions are fascinating.

The process approach advocated by Kaplan for neuropsychological assessment is beautifully presented. The chapter is full of clinical pearls and abounds with figures and illustrations that perfectly make Kaplan's points about different types of cognitive failure. In short, Kaplan attempts to quantify subtle aspects of neurobehavior that are usually deemed qualitative. She discusses in depth her modifications of such well-known tests as block design, digit symbol coding, and the Rey figure. For instance, in block design she has found that breaking the configuration of a design is often associated with right hemisphere lesions. In digit symbol coding, she includes versions that assess purely motor speed, learning, and attention in order to break down the task into its cognitive components.

Using valid and invalid cues to measure covert shifts of visual attention, Posner demonstrates how "disengage, move, and engage" operations are mediated by the parietal lobe, midbrain, and thalamus. All studies use reaction time as a measure. Posner extends his interest in automatic and effortful aspects of attention in an elegant study of the successive cortical systems involved in reading silently, reading aloud, and generating uses for words. Posner also reports on his recent studies on schizophrenia in which he detected an abnormality involving the right visual field and the left anterior brain. These results have provoked controversy because it is unclear if they reflect a lateralized "lesion" or a bilateral "lesion" superimposed on a lateralized function.

All of the authors included in this book have made seminal contributions to the study of the relation between brain and cognition. The book will be especially worthwhile to advanced graduate students in neuropsychology and residents in psychiatry and neurology. Practitioners and researchers can gain important information from the lectures as well and have their theoretical ideas on how the brain works challenged in chapters presented with style and erudition.

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**Contemporary Neuropsychology and the Legacy of Luria,** *edited by Elkhonon Goldberg. Hillsdale, N.J., Lawrence Erlbaum Associates, 1990, 270 pp., $45.00.*

It would seem that it should be an easy matter to assemble a volume in honor of A.R. Luria. His interests were diverse, and his reliance on theory was explicit. Furthermore, he was able to inspire not only respect and admiration but also loyalty and affection. Contributors to the present volume either studied under his direction or believe that they apply his approach to neuropsychological analysis. In every case an interesting piece of work or thought is presented. And yet it cannot truly be said that any of these articles presents a continuity of Luria's approach, let alone the activity of a "school" inspired by him. This is because although Luria's clinical insights were often inspired, they were not based on the detailed experimental analysis and consideration of alternative explanations that are currently considered necessary in the science of neuropsychology.

Beyond advocating a process-oriented approach to case analysis, which many did before him, Luria has not initiated any new direction in neuropsychology. Three fine essays (by Goldberg, Cole, and Sachs) deal with Luria as a "cultural psychologist." Interesting as this perspective is, none of the empirical contributions to this book adopted it. The major theoretical statements—by Brown, Vaughn, and Goldberg—do not derive from Luria. It is revealing that no contributions take sides in any controversy in which Luria might have been involved. The two approaches that were dominant during his lifetime, the psychometric group comparison and the rigid connectionism, outlived him. If they are now in retreat it is because of advances in neurophysiology and cognitive science, many of which Luria foresaw but did not assist.

Luria's relative isolation in Moscow explains much of this. His legacy of insights and of the quality of character remains alive and well. The excellent book under review is witness to this fact.

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**Neuromethods, vol. 17: Neuropsychology,** *edited by Alan A. Boulton, G. Baker, and Merrill Hiscock. Clifton, N.J., Humana Press, 1990, 400 pp., $79.50.*

Neuropsychology is at the crossroads of the behavioral sciences (psychology and linguistics) and the neurosciences (neurology, neuroanatomy, neurophysiology, neurochemistry) and like them has experienced an exponential growth in the last few decades. New methods and technologies have revolutionized this field and provide, for the first time in history, the possibility of taking a look inside the "black box."

Some spectacular and revealing experiments (e.g., with the split-brain patient), together with the impact of the powerful and sophisticated brain-imaging technologies, may give a distorted sense of simplicity about the human mind, especially to the lay public (remember all the pop psychology about hemispheric capacities). Moreover, these experiments and technologies might lead to the naive belief that looking at fancy positron emission tomography (PET) scans will straightforwardly reveal the mysteries of the brain when nothing could be less true. This book is especially useful in pointing out the cautious attitude and the extreme rigorousness needed to deal with such powerful tools. Rigorousness is also needed in the experimental designs and interpretation of results.

The first three chapters review historical developments as well as recent contributions to neuropsychology from neurology, psychiatry, anatomy, physiology, psychology, and linguistics. The next two chapters focus on new brain imaging techniques (CT, magnetic resonance imaging, and PET). The authors give technical information about these techniques and stress methodological issues in order to avoid several common pitfalls. The following chapters address the description of techniques related to the surgical treatment of epilepsy: intercarotid sodium amobarbital, electrical stimulation of the cortex, and the testing of the commissurotomy patient. Eran and Dahlia Zaidel and Joseph Bogen provide comprehensive coverage of the methods and basic issues for examining the split-brain patient.

The differential competence of the left and right hemispheres in different—non-split-brain—populations is summarized in the next chapter by John Bradshaw, who writes a masterly account of the experimental modalities (visual, auditory, tactile) and the complex methodology related to them. Neuropsychological assessment is also reviewed, and both theoretical and practical critical insights are given about "fixed" (e.g., Halstead-Reitan) and "flexible" (e.g., Luria-Christensen) test batteries. The last chapter deals with developmental neuropsychological assessment. The authors propose a systemic approach and dedicate most of the chapter to the exposure of a rationale for the neuropsychological analysis of the child.

This book is not an exhaustive review of the field, and the editors clearly say so in the preface. However, the addition of two more chapters, one on neurophysiological methods and one on neuropharmacological manipulations, would have practically completed the scope of human neuropsychological research.

In conclusion, the effort of the editors in gathering such relevant and appropriate contributions is welcome. The book will be interesting and useful for the clinical psychologist and, obviously, for the neuropsychologist, psychobiologist, and psychophysiologist. What about the psychiatrist? Certainly, there are few references about schizophrenia, depression, or anxiety in this work. Beyond the interest in clinical cases of interface between neuropsychology and psychiatry, the psychiatrist will find in the neuropsychological methods and theories a large and heuristic ground for rethinking and reexamining the classical psychopathological conditions. So I do believe that this can be a revealing and profitable book for many psychiatrists.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Nicotine Cessation, Mania, and Depression

SIR: I would like to report two cases of severe mood disorder following nicotine cessation. It is well known that medical conditions sometimes cause mania and depression. A recent case report (1) suggested that nicotine cessation may have caused a manic episode, but renal failure may have been a confounding factor.

At the urgings of her husband, a 37-year-old woman abruptly stopped a 20-year, one and a half pack per day smoking pattern. One week later, she gradually developed increased energy with inability to sleep. She made phone calls in the middle of the night, felt euphoria ("better than on my wedding day") mixed with terrible sadness. Her sex drive increased and thoughts raced. Inappropriate talkativeness at work, grandiosity, crying spells, and paranoid delusions led supervisors to refer her to our clinic 3 weeks after symptom onset. She had a history of alcohol dependence but had been sober for the past 6 years. There was no prior affective illness. She took no medications. Medical evaluation, including thyroid function tests, drug screen, chemistries, blood count, antinuclear antibodies, neurologic examination, and brain CT scan, was normal except for slightly enlarged lateral ventricles on the CT scan. She remained abstinent from alcohol. Over the course of 1 month she responded to haloperidol and lithium. She resumed normal functioning on a regimen of lithium.

A 48-year-old man without prior mood disorder stopped a 30-year, two pack per day smoking pattern over 3 weeks, and 2 weeks later became profoundly depressed. He lost interest in his family and work, ruminated constantly about suicide, and lost his usual sense of humor. He consistently suffered insomnia with prominent early waking. He was not abusing alcohol or illegal drugs. He took no medications. After 1 month of suffering these symptoms, he sought medical care. Medical evaluation, including CBC, chemistries, neurologic examination, thyroid function tests, chest X-ray, and drug screen, was unremarkable. He was treated with fluoxetine, and within 1 month his depression resolved.

Nicotine cessation among heavy smokers leads to a characteristic withdrawal syndrome. This withdrawal manifests itself in EEG changes (2), possibly suggesting changes in a neuroadaptational state induced by nicotine. Moreover, smoking seems prevalent among patients with a history of major depression, and these patients during nicotine abstinence commonly suffer depressed mood and failure to quit smoking (3). Perhaps this is similar to the dysphoria suffered during withdrawal from other stimulants.

In these cases, major depression and dysphoric mania followed briefly after nicotine cessation. It is difficult to know if this represented causation or an epiphenomenon. Nicotine cessation may be a clinical parameter to investigate among patients with mood disorder.

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## Fluoxetine, Suicidal Ideation, and Aggressive Behavior

SIR: Recently there has been much discussion regarding the possibility that suicidal ideation (1, 2) or aggressive behavior (3) may be associated with fluoxetine pharmacotherapy. I wish to report the case of a patient whose response to learning of fluoxetine's potential dangers was dramatic.

Ms. A was a 62-year-old woman with a 5-year history of recurrent depressive episodes. At least one of these episodes was of psychotic proportions. There was no history of suicide attempts nor was there history of aggressive behavior. There was also no history of obsessions, compulsions, or agoraphobia. The patient had a history of incomplete response to various types of pharmacotherapy for depression but had done well for 10 months while taking fluoxetine, 20 mg/day. One month prior to the hospitalization described here, the patient saw two daytime audience participation television programs in close proximity to each other devoted to the dangers of fluoxetine. Although she had been satisfied with her response to fluoxetine before viewing the programs, she concluded, "There must be something to it." In particular she was concerned that she would "go berserk" and violently attack her grandchildren. Based on this conviction, she discontinued medication abruptly after viewing the second program. During the month after stopping medication, she stayed at home and limited her opportunities for contact with her grandchildren so she would not harm them. She stopped watching television due to a fear that she might see more programs discussing the dangers of fluoxetine and be stimulated to perform violent acts or, perhaps, self-destructive acts. She eventually limited her activity to the point of becoming bedridden out of a fear of her potential for violence. At this point, her children persuaded her to accept an evaluation at a psychiatric emergency room.

She presented with complaints of depressed mood, poor energy, initial insomnia, poor appetite, and poor mental concentration. She denied hallucinations. She recognized that her fears had become unrealistic and had led to great impairment in her functioning. She agreed to hospitalization and to resume fluoxetine treatment at her children's request due to her history of good response to this medication compared with other types of pharmacotherapy. Over a 3-week period there was complete resolution of her symptoms of depression. At discharge she was euthymic and confident about her treatment. She agreed to avoid making unilateral treatment decisions in the future.

There have been reports of other patients suffering rapid deterioration after discontinuing fluoxetine in response to television programs depicting fluoxetine's hazards (3). I do not know of any reports of patients so quickly developing this patient's degree of social isolation due to a fear of becoming aggressive. By history, it was clear that this patient experienced a severe depressive relapse during the month after abruptly stopping medication. Furthermore, the depression contributed to her growing conviction that she was a person capable of doing great harm. Physicians prescribing fluoxetine would do well to solicit regularly any concerns patients may have regarding this highly publicized medication.

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## Penile Anesthesia and Fluoxetine

SIR: I read with great interest the letter by John R. Neill, M.D., (1). I have had a similar case in which a patient complained of penile anesthesia associated with low-dose fluoxetine.

Mr. A was a 47-year-old man with a past history of ethanol abuse and depression who presented to me with a general state of anhedonia, loss of energy, difficulty sleeping, and problems with concentration and attention. At this point, Mr. A denied difficulties with erection, ejaculation, penile anesthesia, or sexual pleasure during intercourse. Other than a loss of libido associated with his depression, Mr. A denied specific sexual difficulties. Mental status examination revealed a male whose mood was apprehensive and indifferent with a flat and depressed affect. His past medical history was remarkable only in that he had a cardiac pacemaker implant because of conduction difficulties. For this reason, he was started on a regimen of fluoxetine.

The patient responded well to 20 mg/day of fluoxetine. After 4 weeks, during a routine medication check, he reported penile anesthesia associated with sexual intercourse. This particular side effect did not seem to be ego dystonic to the patient, so he chose to continue at the prescribed dosage. After approximately 3 months of treatment with fluoxetine at 20 mg/day, Mr. A developed ejaculatory difficulties. The dose was decreased to 20 mg every other day, after which the ejaculatory problems dissipated, but the penile anesthesia continued. Approximately 4 weeks after this, there was a recurrence of Mr. A's depressive symptoms, and once again, after consultation with the patient, the fluoxetine dose was increased to 20 mg/day. At this point treatment with cyproheptadine was considered, but the patient elected not to try this medication, as he felt the ongoing depression was a greater problem than his fluoxetine-associated penile anesthesia.

My review of the available literature and discussion with the manufacturer of fluoxetine showed no previous reports of penile anesthesia associated with its use. The report by Dr. Neill, taken in light of my patient's report, suggests a spectrum of side effects of sexual dysfunction associated with the use of fluoxetine, from penile anesthesia to anorgasmia.

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## Capgras' Syndrome and the Mignon Delusion

SIR: Recent years have witnessed a resurgence of interest in delusional misidentification syndromes, especially Capgras' syndrome. Over the years since Capgras and Reboul-Lachaux (1) first described this uncommon delusion, many different psychodynamic, as well as organic, and most recently cognitive (2), theories have been set up to explain it.

Here we report the interesting case of a chronic schizophrenic patient, the natural history of whose delusions might shed some light on the dynamics underlying some cases of Capgras' syndrome.

Mr. A, a 19-year-old man suffering from chronic schizophrenia in an acute exacerbation, was brought to our outpatient clinic by his family and was subsequently admitted. His illness had run a deteriorating course in the years since its onset, with two previous admissions.

On admission he was depressed and agitated with prominent persecutory and grandiose delusions. His delusions on the previous admission had included the false belief of being the offspring of other parents of a higher station (Mignon delusion), and the belief that he had been kidnapped and sold to his present parents at the age of 5. In the present admission he demonstrated a bizarre form of the Capgras' delusion, maintaining that his "adoptive" family had been replaced by a group of "foreign doctors." He asserted that these impostors, whose mission was both to look after and spy on him, looked exactly like the original persons. He also complained of being changed physically by his persecutors, so that his true origins might not be detected. Other symptoms in his mental status examination included déjà vu experiences merging into delusional memories and the delusion of being controlled by external forces.

Successive drug trials with trifluoperazine, 30 mg/day; haloperidol, 30 mg/day; and thiothixene, 30 mg/day, failed to remove his delusions but ameliorated his depression and agitation.

Organic pathology is implicated in many cases of the Capgras' syndrome. However, our patient was free of such pathology. Results of the physical and neurological examinations were normal, as were his blood biochemistry, a CT scan, an EEG, and the Bender-Gestalt test.

The sequence of the development of this patient's delusions, running parallel to the gradually deteriorating course of his illness, suggested that his Capgras' delusion might have been a more emphatic, as well as a more bizarre, form of denial of relationships than is the case with the Mignon delusion. Thus, in this case, the Capgras' delusion might be regarded as a more "psychotically" elaborated form of the same theme as that of the Mignon delusion.

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### Kerosene Abuse By Inhalation and Ingestion

Sir: Chronic solvent abuse is associated with high morbidity and mortality (1) and hence warrants special attention. From India, the only published report is by Mahal and Nair (2), which describes dependence on petrol. We wish to report here an unusual case of kerosene abuse by inhalation and ingestion seen in New Delhi.

Ms. A, a 17-year-old student, presented with an 8-month history of kerosene use. Swallowing half a teaspoonful the first time, she enjoyed the tingling sensation in the mouth and the heady feeling. Subsequently she started inhaling it also. Inhalation from a large container would occur almost daily for up to 60 minutes, and ingestion alone would occur once in about 15 days.

The effects experienced were anxiety, nausea, and euphoria lasting for approximately 15, 30, and 90 minutes, respectively. Effects described were feeling intoxicated, "high," and powerful, of thoughts flowing fast, and occasionally, feeling fearful. Time appeared to move fast and her body felt lighter. There was a subjective sense of "confusion," mild headache, and a buzzing sound in the ear, lasting up to 6 hours. All these effects were shortlasting and temporally related to kerosene use. Occasionally she would feel drowsy and go off to sleep. There was no history of cognitive deficits, disorientation, or any symptoms to suggest toxic psychosis. There was no sustained mood change, grandiosity, or any other symptom suggestive of mania beyond the point of intoxication. During a period of abstinence she experienced anxiety, irritability, nausea, and abdominal pain lasting for about 5 days. Craving continued to be present even after 3 weeks of withdrawal.

Ms. A's blood chemistry, liver function test, chest X-ray, ECG, and EEG were within normal limits. Urinary porphyrins, basophilic stipling in blood, and occult blood in stool were absent. The only abnormal finding in our investigation was a hemoglobin level of 9.4 g/dl which was probably due to a nutritional cause. This is common in India, especially among women. A diagnosis of inhalant abuse (kerosene) according to *DSM-III-R*, axis I, and disorder resulting from the use of volatile solvents (harmful use, mild) according to *ICD-10* (1989 draft) was made.

The patient, though fulfilling the criteria for inhalant/solvent abuse, differed from the typical cases described in published reports in many ways. Kerosene is an unusual substance to be abused by a woman, especially with the mode of abuse being ingestion and inhalation. The literature describes male preponderance (3, 4), group activity (3), and inhalation as the preferred mode. Evidence of conduct disorder, antisocial personality traits, family disruption, and use of other psychoactive substance use was absent.

Drug abuse/dependence has shown a considerable increase in India in recent years (5). However, cases of solvent abuse are rarely encountered, possibly because most epidemiologic studies do not include questions for eliciting solvent abuse nor routine inquiry of clinical patients about drug abuse. These factors could be partially responsible for the scarcity of reported cases of solvent abuse. In view of the increasing prevalence of this problem in other countries and serious morbidity and mortality in adolescents abusing solvents, this area needs special attention in the future.

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### Treatment of Pathological Gambling With Clomipramine

Sir: Pathological gambling is a common psychiatric disorder (1) with considerable morbidity and mortality (2). Nevertheless, for the most part it is a neglected disorder, with few controlled studies of its causes or treatment. Given the high rates of comorbid substance abuse, depression, and suicide, pathological gambling is a major public health problem (1, 2). Current treatments for pathological gambling include cognitive-behavioral approaches (3), self-help groups (4), and inpatient or rehabilitation programs (5). However, many patients remain refractory to treatment (3–5), and more effective treatments are needed.

While pathological gambling is currently classified as a disorder of impulse control, many patients and support groups consider it to be a compulsive disorder. Pathological gambling has also been considered to be related to obsessive-compulsive disorder. The following case describes the double-blind, placebo-controlled treatment (10 weeks for each phase) of a pathological gambler with clomipramine, a partially selective serotonin reuptake blocker marketed for the treatment of obsessive-compulsive disorder.

Ms. A was a 31-year-old woman with a 12-year history of pathological gambling. She also had a history of discrete social phobia (fear of public speaking) and mild obsessive-compulsive personality features (including perfectionism and hoarding) which did not meet *DSM-III-R* criteria for obsessive-compulsive personality disorder. The pathological gambling behavior consisted primarily of playing cards, numbers, bingo, and slot machines and occurred 2–3 times per week. Consequences of gambling included losses of up to $600 per day, loss of her apartment due to financial ruin, and loss of several jobs because she had been up all night gambling. Previous treatments included participation in Gamblers Anonymous for 3–4 years, which resulted in abstinence from gambling for the first year and a half. Other treatments included outpatient psychotherapy for 1 year, which was considered helpful, but did not result in discontinuation of gambling. Prior to current treatment, she had been gambling consistently for 6 1/2 years.

Treatment included a double-blind, placebo-controlled trial of clomipramine. At week 10 of the placebo trial, the clinician's global improvement change score was 3 (minimally improved), and the patient self-report was 25% improved. Gambling continued during this phase. Clomipramine was initiated at a dose of 25 mg/day and increased by 25 mg every 3 days to 150 mg/day. Due to the development of irritability, the dose was decreased to 125 mg/day. At week 10 of the clomipramine trial, the clinician's global improvement change score was 1 (very much improved), and the patient self-report was 90% improved. The gambling behavior discontinued by week 3 and remained in remission throughout the duration of the trial. Except for a brief relapse at week 17, the gambling remained in complete remission for an additional 28 weeks of open clomipramine treatment (175 mg/day).

This case is reported to demonstrate the possible efficacy of clomipramine in the treatment of pathological gambling. Further placebo-controlled, double-blind trials of clomipramine in large patient samples are needed to confirm the efficacy of this approach in the treatment of this major public health problem.

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## Sinus Bradycardia Related to the Use of Benztropine Mesylate

Sir: We present a case of a paradoxical effect of benztropine mesylate manifested by sinus bradycardia in a patient with normal cardiac function. To the best of our knowledge this is the first such report.

Mr. A was a 50-year-old man hospitalized for severe depression with psychotic features. He had a history of bipolar affective disorder with frequent (2–3 times/year) hospitalizations since age 20. The patient received lithium, antipsychotics, antidepressants, and antiparkinsonian drugs over the course of years. His medical history was unremarkable except for hypercholesterolemia. On admission his heart rate was 108 bpm and his blood pressure was 149/100 mm Hg. The findings on physical and laboratory evaluations were normal. The patient was started on a regimen of lithium carbonate, 600 mg/day; haloperidol, 10 mg/day; bupropion, 75 mg/day; and benztropine mesylate, 2 mg/day. Because of the severity of the suicidal ideation and agitation, haloperidol was increased to 15 mg/day, and the benztropine dose was increased to 3 mg/day.

The next day bradycardia was detected with a pulse rate of 50 bpm. The blood pressure was 106/60 mm Hg. The ECG showed sinus bradycardia. The same day bupropion was discontinued. The bradycardia continued and became more pronounced the next day, when the heart rate dropped to 40 bpm and blood pressure to 90/70 mm Hg. An acute myocardial infarction was ruled out, and therefore an adverse drug reaction was suspected. Haloperidol was decreased to 10 mg/day and benztropine to 2 mg/day, while the lithium dose remained the same. The bradycardia persisted as evidenced by Holter monitor, with a minimum rate of 33 bpm and an average of 43 bpm. At this time benztropine was discontinued, as it was a possible cause of bradycardia, while haloperidol and lithium doses remained the same. In subsequent heart rate monitoring, a return to normal values was observed, with the heart rate stabilizing between 60 bpm and 84 bpm over the next 48 hours.

Our case report indicates the possibility of a paradoxical effect of benztropine on heart rate. Bradycardia in response to atropine (1) and trihexyphenidyl (2) was described previously. It has been suggested that the decrease in heart rate could have been produced through a blockade of $M_1$ receptors on postganglionic parasympathetic neurons, which differed from the effects of postsynaptic $M_2$ receptor blockade on the end organ (myocardium) (1, 3). In the case presented here, the unusual reaction to the commonly prescribed drug may have been due to the patient's altered receptor sensitivity as a result of his long-term exposure to anticholinergic drugs or to a drug combination.

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## Acute Depressive Symptoms After Mefloquine Treatment

SIR: Mefloquine, a 4-quinolinemethanol derivative, is an effective drug for the prophylaxis and treatment of multiresistant plasmodium and falciparum malaria. Reversible adverse neurological reactions are well known. They include cognitive disturbances with memory impairment, confusion, and seizures (1, 2). Recently, acute psychotic symptoms such as delusions and visual hallucinations were reported by Stuiver et al. (3) and "confusion with depression" was reported by Bjorkman (4). It is estimated that 40% of patients under mefloquine treatment experience psychosis (3). Considering the increasing risks of contracting multiresistant malaria due to greater resistance of the illness to treatment and more frequent overseas travel, psychiatrists must be aware of depressive states as an adverse effect of mefloquine. To the best of our knowledge, these are the first reported cases of acute depressive symptoms after mefloquine treatment of patients without previous psychiatric history or known recent stressful events.

> Ms. A, a 33-year-old woman, was spending her holidays in Thailand. After her third weekly prophylactic dose of mefloquine, 250 mg, depressive symptoms occurred, starting with insomnia. Seventy-two hours after the beginning of the sleep disorders, she became sad and wept easily. The symptoms, including motor retardation and apathy, were constant for 5 days. She recovered spontaneously.
>
> Mr. B, a 24-year-old man on vacation in Mali, was receiving prophylactic chloroquine, 100 mg/day. He had a fever. Fearing acute malaria, he was treated with a first curative dose of mefloquine, 750 mg. The first symptoms then occurred, including insomnia, anorexia, and loss of weight (6 kg). Although no evidence of malaria had been found, a second dose of 750 mg of mefloquine was given. In the next few days he suffered panic attacks and cognitive disturbances and contemplated suicide. Because of the high risk of suicide, he was admitted to a psychiatric ward. He received an antidepressant (clomipramine, 100 mg/day for 40 days) and returned to normal in 10 days.

In both cases, following a cumulative dose of mefloquine, 750 mg, the first symptom was insomnia. Depressive symptoms were of short duration in spite of the long half-life of mefloquine (13 to 26 days) and characterized by favorable evolution and lack of residual disorders. No delusions or hallucinations were observed.

Although, of course, psychiatric vulnerability cannot be excluded, two pharmacologic hypotheses are worth discussion. 1) As with other chloroquino-derivative antimalarial drugs, direct urological toxicity can be suspected. But plasma levels of mefloquine acsertained in patient B showed a value of 260 ng/ml in the therapeutic range (10–1000 ng/ml). 2) Indirect toxicity is also a possibility. The main metabolite of mefloquine, quinoline 4 carboxylic acid, does not cross the blood-brain barrier, but other metabolites could be involved. Further studies investigating the pharmacologic process of depressive symptoms with mefloquine treatment are necessary.

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## Trazodone Induction of Migraine Headache Through mCPP

SIR: We would like to report a case in which a patient suffered severe migraine headache symptoms after being treated with trazodone.

> Mr. A, a 35-year-old man with a 7-month history of lower back pain was referred to the first author's clinic for evaluation and treatment of depressive symptoms. The patient had a diagnosis of chronic myofascial pain syndrome, and on examination, he met *DSM-III-R* criteria for major depression. He had no history of previous chronic pain.
>
> The patient was started on a regimen of doxepin; however, in the second week of treatment, he developed anticholinergic side effects. These disappeared after doxepin was stopped, and 1 week later he started taking trazodone. The initial dose was 50 mg h.s., which was increased to 100 mg h.s. after week 1 and to 200 mg h.s. after week 2. On day 3 of the 200 mg dose, the patient developed severe nausea, vomiting, and right central scotomata. These symptoms were followed by a severe, throbbing, right frontotemporal headache (unlike any the patient had previously experienced), accompanied by severe photophobia and right facial numbness. Mr. A was taken to a local emergency room for evaluation where CT scans, with and without contrast, were negative. A consulting neurologist diagnosed classic migraine, new onset. Trazodone treatment was stopped, and after 1 week the patient was started on desipramine, with resolution of his depression within 1 month. At 3- and 6-month follow-ups, the patient reported no recurrence of headaches, with the exception of one 30-minute episode of frontal headache which was responsive to acetaminophen.
>
> When Mr. A was seen following his headache episode, additional history indicated that his aunt and sister suffered from headaches which were responsive to sublingual ergotamine. Also, the patient reported that as a child, he frequently experienced "car sickness," a finding which is common among migraine patients. These data suggest a genetic predisposition toward migraine, which may have been stimulated by trazodone.

Trazodone's major active metabolite is m-chlorophenylpiperazine (mCPP), which is a potent nonselective serotonin receptor agonist (1). Serotonin releasing factor has been found to be present during acute migraine attacks, and serum serotonin has been shown to be increased during such attacks (2). Cerebral vessels (whose constriction and dilation are involved in migraine mechanisms) are highly innervated by serotonin fibers from the raphe nucleus (3), and this is the likely basis of the antimigraine effectiveness of serotonin antagonists such as methysergide. Also, sumatriptan, a presynaptic serotonin $5\text{-HT}_{1D}$ autoreceptor selective agonist, has powerful antimigraine effects, apparently through its ability to enhance serotonin reuptake and thus inhibit net serotonin transmission (4). More directly relevant to this case report is prior evidence that mCPP itself can induce migraine symptoms in humans (5).

Although headache (type unspecified) is reported as a side effect of trazodone in the *Physicians' Desk Reference*, this is, to our knowledge, the first report linking this agent to vascular headache. Trazodone, through its metabolite mCPP, may potentially induce migraine symptoms in genetically susceptible patients. A detailed family history of migraine headaches, as well as a personal history and related symptom history, should be obtained from candidates for trazodone treatment.

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## Laterality of Torsion in Tardive Dystonia

SIR: The study of the laterality of drug-induced movement disorders may have significant implications for the underlying neurobiology of schizophrenia and the mechanism of action of neuroleptic drugs. Studies of tardive dyskinesia in schizophrenic patients have reported a predominance of involuntary movements to the right in two studies, to the left in one, and equally to the right and left in one (1). Studies of neuroleptic-induced parkinsonism suggest a tendency for the left striatum to be hypersensitive to dopaminergic blockade, resulting in a greater degree of right-sided parkinsonism (2). Two single case reports of tardive dystonia in schizophrenia (3, 4) reported a right-sided rotation.

We have examined six patients with tardive dystonia in our clinic who had an axial dystonia with a rotational component and found a greater tendency for a right-sided rotation. All were right-handed. Five had a schizophrenic disorder. Two patients had rotation of the head to the right, one with the additional involvement of the right arm. With the third patient, although there was bilateral involvement, the movement of the head was predominantly to the right. The fourth patient had bilateral turning of the head, flexion of the trunk to the right, and involvement of the left arm. The fifth patient had head rotation to the left and involvement of the right arm. The sixth patient, who suffered from a bipolar affective disorder, had bilateral involvement of neck muscles with left-sided involvement more than the right, producing a greater tendency to rotate to the right. Three of these patients had orolingual dyskinesias which were bilaterally symmetrical on clinical inspection.

Evidence from animal studies suggests that the direction of rotation may reflect an asymmetry of striatal dopamine function. Some evidence for increased asymmetry in striatal dopamine receptors in schizophrenic subjects, as compared to normal control subjects, exists from post-mortem studies, with a reported greater density on the right (5). Whether this was caused by previous neuroleptic medication or the disease process itself remains uncertain. The evidence for the prominence of neuroleptic-induced parkinsonian symptoms on the right side (2) argues for relative hypodopaminergic activity in the left striatum. The right-sided prominence of tardive dyskinesia and the greater likelihood of rotation to the right in tardive dystonia are more difficult to interpret in the absence of a clear understanding of the pathophysiology of these disorders and considering the controversy that still exists regarding the cerebral representation of neck rotation. Our cases, therefore, lend further support to the asymmetry of neuroleptic-induced side effects but do not help settle the following questions: Are these asymmetries the result of the asymmetric action of neuroleptics on a neurochemically symmetric brain, or vice versa? Or are they indeed a combination of two asymmetries? Are the side effects asymmetric only in schizophrenia? Answers to these questions can only be obtained by investigating larger groups of patients suffering from different psychiatric disorders with in vivo functional imaging and detailed post-mortem neurochemical assessments.

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## Oxytocin and Vasopressin in Obsessive-Compulsive Disorder

SIR: A growing body of literature suggests that oxytocin and vasopressin have a significant effect on behavior, mood, and memory. More recently, it has been reported that oxytocin administration ameliorates obsessive-compulsive disorder symptoms (1, 2) and that CSF concentrations of the two peptides are altered in the disorder (3, 4). We hypothesized that these alterations might be etiologically related to obsessive-compulsive disorder.

In order to evaluate the effects of brief peripheral administration of oxytocin and vasopressin on obsessive-compulsive disorder symptoms, three patients with the disorder (two male, one female) were administered, in blinded, random order, intranasal oxytocin (Syntocinon; two sprays deliver approximately 8 IU), intranasal vasopressin (80 IU of desmopressin), and normal saline. A second dose of each substance was given after 90 minutes. Patients were rated for changes in mood, memory, and obsessive-compulsive disorder symptoms at 5–30-minute intervals (chosen to correspond with periods of peak drug activity) for a total of 3 hours. Standardized visual analog scales were used to rate mood, general anxiety, global functioning, and degree of obsessionality and compulsivity (5), and digit span tests were administered to assess memory.

There were no discernible effects of vasopressin or oxytocin on any of the physician or patient ratings of obsessive-compulsive disorder symptoms, mood, or anxiety; nor was digit span appreciably affected by the drugs. One patient spontaneously reported feeling irritable and nervous within 2–3 minutes of vasopressin administration, and this discomfort persisted for over 90 minutes; however, she had similar (albeit milder) complaints following a subsequent normal saline challenge. Another patient, who had not noted any effects of normal saline or vasopressin, felt that oxytocin decreased his compulsions and stated, "I didn't check or count my steps when I left the bathroom just now— that's the first time in as long as I can remember." This was not reflected in his self-ratings, however, and when oxytocin administration was repeated in his home environment, it had no appreciable effect.

Although the methodology and sample size of this pilot investigation were severely limiting, the results suggested that obsessive-compulsive disorder symptoms were not responsive to brief oxytocin or vasopressin administration. The question of whether or not long-term administration of either of these peptides will be effective for obsessive-compulsive disorder and whether abnormalities of these neurohormones play a role in the onset of the disorder remain unanswered. Additional, controlled studies utilizing biological measures of pharmacologic activity, a range of drug dosages, and longer treatment periods may be indicated to ascertain whether or not abnormalities of oxytocin and vasopressin are directly related to obsessive-compulsive disorder.

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## Acute Pancreatitis Associated With Clozapine Use

SIR: The atypical antipsychotic agent clozapine has a unique profile of side effects, which are likely to appear soon after treatment is begun and can limit its use (1). Many of the drug's complications are gastrointestinal, and clozapine has been observed to induce transient elevations of serum bilirubin and amylase (2). A patient of ours developed acute pancreatitis shortly after starting treatment with clozapine. We postulate that acute pancreatitis may be associated with clozapine use.

Mr. A, a 40-year-old man with moderate mental retardation and bipolar disorder refractory to neuroleptics, carbamazepine, and lithium carbonate, was started on a regimen of clozapine in the hope of treating his psychotic symptoms and progressive tardive dystonia.

His other antipsychotics were tapered and discontinued and clozapine was initiated at a dose of 25 mg/day. The dose was increased as permitted by postural heart rate and blood pressure changes. By the eighth day, he was receiving 150 mg/day. On the ninth day his temperature was 101.3 °F, his abdomen was mildly distended, and bowel sounds were hyperactive. Rectal examination revealed retained feces. Transient defervescence and overall improvement followed the application of enemas and laxatives. Laboratory results were within normal limits, and clozapine was continued. On the twelfth day the patient's condition again deteriorated. After three episodes of biliary emesis, his rectal temperature was 101.7 °F, and his abdomen was diffusely distended, typanitic, and tender. The rectal vault was again impacted with feces.

Abdominal X-rays showed a large amount of colonic stool and scattered air-fluid levels. Laboratory results included a normal amylase level and a WBC count of 8800/mm$^3$, with 29% bands; and the patient was treated for fecal retention. Clozapine was discontinued, however, and 36 hours after the patient's last dose, a serum lipase level of 4380 U/ml first suggested the diagnosis of pancreatitis. Amylase and lipase levels progressively rose to peak values of 343 U/ml and 5178 U/ml, respectively. CT scan of the abdomen confirmed pancreatic inflammation and edema.

Both CT scan and abdominal ultrasound demonstrated a normal pancreatobiliary tree and no evidence of gallstones. Despite a complete workup, no cause could be found for the pancreatitis. Mr. A's clinical condition rapidly returned to normal after the discontinuation of clozapine.

The patient in this case suffered an attack of acute pancreatitis during the second week of treatment with clozapine. This could have been purely coincidental, but clozapine was clearly suspect.

Clozapine is known to act on the salivary glands to produce sialorrhea through poorly understood mechanisms (3). The salivary glands and the pancreas share a common vulnerability to toxic agents (e.g., alcohol), to metabolic derangement (e.g., hyperchylomicronemia), or to immunologic attack (e.g., mumps) (4). It can be speculated that clozapine has exocrine and probably toxic effects on both salivary and pancreatic tissue. This hypothesis awaits confirmation from other clinical cases or laboratory studies associating pancreatitis with the drug.

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## Battered Woman Syndrome

SIR: Since the 1970s, increasing attention and study has focused on the phenomenon known as the "battered woman syndrome." Over the last 15 years, a growing body of literature has accumulated on this topic, leading to a general acceptance in the mental health community of the legitimacy of this syndrome. As our knowledge in this area has grown, the courts have begun to recognize the battered woman syndrome as a defense, in part or whole, to charges of murder and related offenses when a woman slays her assailant after having been previously brutalized by him. Mental health professionals have provided invaluable assistance to courts by explaining the otherwise perplexing phenomena seen in battered women, such as why they do not leave their abuser and why they may subjectively believe their lives to be in danger even when their assailant is asleep. Many jurisdictions now allow expert testimony to determine whether the woman was suffering from the battered woman syndrome, which may negate the specific intent required for the offense charged, mitigate the sentence of the convicted defendant, or completely exonerate the woman for acting in self-defense based upon her honestly held, subjective belief that her life was in danger.

Although this letter is not intended to criticize the legitimacy or the importance of recognizing the battered woman syndrome, I evaluated a woman charged with the murder of her husband, who allegedly had severely abused her, in a jurisdiction in which proof of the battered woman syndrome would have led to a complete defense and a finding of not guilty. I determined that the woman was malingering. A review of the literature resulted in finding absolutely no review articles, research, or case reports documenting malingering in the battered woman syndrome.

I based the diagnosis of malingering on numerous inconsistencies involving the crime scene, statements to the police, demeanor inside and outside the clinical interviews, past psychiatric history, past alcohol and drug history, sexual history, and personal history. Reliance solely on information provided by the defendant would have led to the erroneous conclusion that she suffered from the battered woman syndrome.

The clinical information on the extent of the battered woman syndrome and its devastating consequences is vitally important to the criminal justice system in assessing culpability. However, since the general public has been exposed to this syndrome and many jurisdictions allow testimony that may mitigate or absolve defendants of criminal responsibility, the clinician and forensic examiner must consider the possibility that the battered woman syndrome may be feigned. Essential to any thorough forensic evaluation is the collection of data from sources other than the defendant. Although no other cases of malingering in relation to the battered woman syndrome appear in the psychiatric literature, I strongly suggest that at least a small percentage of such allegations in criminal proceedings may be false. Only with the reporting of such cases can the prevalence of malingering in the battered woman syndrome be known.

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### Diagnostic Agreement

SIR: It is surprising, perhaps astonishing, that so few studies of diagnostic agreement on *DSM-III* (or *DSM-III-R*) have been reported. Among the few, there are the *DSM-III* field trials reported in 1980 (*DSM-III-R*, pp. 493–496) and an axis II study reported from Australia in 1982 (1).

A true test of diagnostic agreement must meet at least four criteria: 1) The diagnosticians must be clinically qualified to use *DSM-III*, 2) they must not have ordinarily worked together (thus learning each other's "diagnostic habits"), 3) the cases must be selected on some nondiagnostic basis, and 4) the same information must be made available to each diagnostician.

The *DSM-III* study, substantial though it was, failed to control for diagnosticians being familiar with each other's diagnostic predispositions. This is understandable, but even so one must have some assurance that diagnostic agreements are geographically transplantable.

Most studies have shown acceptable diagnostic agreement on broad categories (e.g., schizophrenia and organic mental disorder). An adequate assessment of agreement on finer diagnostic categories is indicated.

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### Correction Rate of Severe Hyponatremia and Central Pontine Myelinolysis

SIR: Our report (1) of a polydipsic schizophrenic patient who survived an episode of severe hyponatremia with status epilepticus induced by hydrochlorothiazide drew responses from Pritesh J. Shah, M.D., and William M. Greenberg, M.D. (2), as well as from Hans Rittmannsberger, M.D. (3), warning of the dangers of central pontine myelinolysis when the correction of hyponatremia is made too rapidly.

Central pontine myelinolysis is the selective loss of myelin involving the center of the basal pons and other extrapontine areas of the brain where gray and white matter intermix. It accompanies many chronic debilitating diseases and is most often seen in malnourished alcoholics. Symptoms of the fulminant state include dysarthria, impaired swallowing, pseudobulbar signs, quadriparesis, and quadriplegia.

The too-rapid correction of hyponatremia has been implicated in a number of cases of central pontine myelinolysis, but the picture is anything but clear. Major ambiguities include whether the severity and/or chronicity of hyponatremia prior to correction contribute to demyelinization and what constitutes a safe correction rate for different degrees of hyponatremia. Hyponatremia is defined as a serum sodium level below 135 meq/liter and is most often mild (serum sodium level above 120 meq/liter) and asymptomatic. Severe hyponatremia (serum sodium level below 120 meq/liter) may lead to severe neurological damage or death.

Our patient was admitted to the intensive care unit unresponsive and in status epilepticus, with a serum sodium level of 108 meq/liter. Treatment with intravenous phenytoin sodium and diazepam did not break the seizure, which resolved only after administration of a short course of 3% saline; this was stopped once the serum sodium level rose to 126 meq/liter (mild hyponatremia). As is common with psychogenic polydipsic patients during fluid restriction, a large free water diuresis developed and continued until the serum sodium level spontaneously reached 135 meq/liter, 8 hours after admission (average rate of bimodal correction=3.4 meq/liter per hour). This rapid diuresis and change in serum sodium may have been potentiated by phenytoin sodium, which is known to inhibit release of ADH from the pituitary.

Two years after this eposode, our patient shows no sign of neurologic damage. A recent review (4) of 13 psychogenic polydipsic patients with hyponatremic seizures showed that 12 of the patients had serum sodium levels corrected "rapidly" to 120–130 meq/liter within 12 hours. In no case was there clinical or radiologic evidence of neurologic sequelae after 6 years of follow-up.

Critically summarizing the literature on the correction rate of hyponatremia, Ayus et al. (5) conclude:

> Severe symptomatic hyponatremia (serum sodium level below 120 meq/liter) is often a life-threatening emergency that can result in permanent neurologic damage or death if left untreated. Early recognition and rapid correction to mildly hyponatremic levels by administration of hypertonic saline are important in order to reduce the potential mortality and morbidity. If the serum sodium level is more than 105 meq/liter, it can be corrected to a value of 125 to 130 meq/liter. Care should be taken to avoid acute correction to normonatremia or hypernatremia.

It is the too-rapid correction of severe hyponatremia to normal or above normal levels (3% saline was stopped at 126 meq/liter in our patient) that appears to hold the greatest risk of central pontine myelinolysis.

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## On Organic Unity Theory

Sir: There has been a recent resurgence of interest among psychiatrists, particularly in the Unitied States, Great Britain, and Germany, in exploring philosophical issues, e.g., the mind-body problem and our notions of psychopathology. One focus has been the reexamination of the biopsychosocial model, as articulated by George Engel (1–3). Aviel Goodman, M.D., in championing "mental-physical identity" as an elaboration of Engel's model, has presented a thoughtful, sophisticated enhancement (4). As welcome as his discussion is, I nonetheless have two critical comments.

Many "identity" and "correspondence" theories of the mind-body problem have been insufficiently characterized in their particulars to be clearly distinguished. Dr. Goodman explicates identity (extensional, intensional, and/or identity in empirical validating evidence), but in telling us that the theory of mental-physical identity pertains to both extensional identity and "metaintensional" hypothesized isomorphic correspondence "between configurational (gestalt) features of the mental conceptual network and certain configurational features of the physical conceptual network" (4, p. 556), he is making a compound claim. This does not, as advertised, "[circumscribe] the mind-body problem . . . to the realm of logical analysis" (4, p. 557) but leaves attached those hypotheses of isomorphic correspondence, plausibly but not necessarily at the neurophysiological level, which are subject to empirical investigation. Dr. Goodman does elsewhere grant this (4, p. 557, 559), but in his thorough explanations we are still left with a doctrine of "identity *and* correspondence," subject both to linguistic conceptual analysis and empirical study. This level of sophistication is fine for the philosopher but brings me to the second stated concern, which is didactic.

Engel, who was clearly antidualistic (2), intended his biopsychosocial model for a wide audience, prominently including mental health profession trainees and nonpsychiatric physicians. He felt that all health professionals needed an alternative to the biomedical model and a handy mnemonic to remind them that the patient is a person with a mind (no dualism intended) and has a family and relevant sociocultural context, obvious verities all too easy to forget when one is intensely trained to address one focused perspective and must evaluate and treat patients quickly (1–3, 5). Mental-physical identity is another important lesson, but I fear that "organic unity theory" lacks the euphony and self-obvious descriptiveness of Engel's wonderfully chosen term, which has also been selected in our current APA presidential theme. Elaborate on Engel's "person (experience and behavior)," but don't rob us of "biopsychosocial" in giving us "organic unity"!

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## Dr. Goodman Replies

Sir: Dr. Greenberg's observation that my formulation is "a doctrine of 'identity *and* correspondence,' subject both to linguistic conceptual analysis and empirical study" is astute and underscores a critical and sometimes difficult distinction. Earlier in the same paragraph, however, his discussion of my ideas blurs this distinction in a way that could promote a misunderstanding of them. He refers to "hypotheses of isomorphic correspondence, plausibly but not necessarily at the neurophysiological level, which are subject to empirical investigation." In my essay, the hypothesis "that there exist isomorphisms between certain configurational (gestalt) features of the mental conceptual network and certain configurational features of the physical conceptual network" (p. 556) is a linguistic/conceptual hypothesis that refers to relationships between conceptual networks; it is not an empirical hypothesis and is not subject to empirical investigation. Hypothesized configurational isomorphisms would be of the following form: If *a* and *b* are concepts in the mental conceptual network, then there exist some concepts *c* and *d* in the physical conceptual network for which the relationship between *c* and *d* is isomorphic with the relationship between *a* and *b* (e.g., *a* is an element of *b*, or *a* is a property of *b*, or *a* occurs after *b*, etc.). This hypothesis is not identical to a hypothesis that variables *a* and *c* or *b* and *d* correspond to each other (i.e., have the same putative referent), and it certainly is not identical with a hypothesis that any specific terms A and C or B and D correspond to each other. Only the last of the three types of hypothesis would be subject to empirical investigation.

Not until the next page and in another context did I introduce the term "correspondence," when I discussed Feigl's "'empirical identifications'—statements functioning as hypotheses of correspondence between phenomenal concepts and physical concepts, the substantiation of which requires empirical evidence" (p. 557). I then proceeded to discuss "the important distinction between mental-physical identity theory and hypotheses of mental-physical correspondence" (p. 557). Mental-physical identity theory describes a relationship between the mental and physical conceptual networks, while a hypothesis of correspondence is a statement that a specific mental concept and a specific physical concept refer to the same event or process. Hypotheses of correspondence are grounded on the putative extraconceptual referent which both the mental and physical terms are hypothesized to designate, and their validation thus depends on empirical evidence. Mental-physical identity theory, meanwhile, remains within the realm of linguistic-conceptual analysis, and its validation depends on its explanatory power rather than on the confirmability of predictions derived from it (philosophers of science are increasingly recognizing the distinction between explanatory power and confirmability of predictions, and that the scientific value of a theory has more to do with the former than the latter [1–3]). Mental-physical identity theory does not necessarily indicate that any hypotheses of correspondence will be empirically confirmed, only that no other kinds of hypotheses relating mental to physical are logically sound.

In response to Dr. Greenberg's comments, I recognize that Engel was antidualistic, and I hope that my contribution helps make his biopsychosocial model more completely consistent with his antidualistic intent. In integrating the biopsychosocial model with mental-physical identity theory, organic unity theory rectifies what I believe was a flaw in the biopsychosocial model that, while subtle, undermined the integrity of the model. Organic unity theory was not intended to detract from or to supplant Engel's pioneering work but rather to supplement it. I also recognize that the concepts of mental-physical identity are difficult to grasp, to a great extent because they contradict the dualistic philosophy embodied in our language, and that they are unlikely to be embraced by the wide audience that has accepted the biopsychosocial model. Please rest assured that robbery is not on my agenda.

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## Clonidine and Stuttering

Sir: John Paul Brady, M.D., recently gave an excellent review of the pharmacology of stuttering (1). He cited Swift et al. (2) who pointed out that haloperidol is helpful in stuttering and in two other disorders which share several characteristics with stuttering: motor tics and Tourette's disorder. Indeed, stuttering is often known to occur in combination with other motor activities such as swallowing, coughing, eye blinking, and grimacing. Comings and Comings (3) reported that 31% of 26 patients with Tourette's disorder stuttered or had stuttered in the past. In our clinical practice with children with Tourette's disorder, we also found the combination with stuttering. Our first choice of medication for children with Tourette's disorder is clonidine, an $\alpha_2$-noradrenergic agonist (4). In the population of those children who showed the combination of Tourette's disorder with stuttering, we observed not only a decrease of tics and hyperactivity but also a decrease in stuttering. Based on these findings, we started an open trial, treating children who stutter with clonidine medication (4 μg/kg per day). The children were referred to our clinic because of their stuttering. No Tourette's disorder symptoms were reported in the children or in their relatives. The group consisted of five boys aged 8–14 years and two girls aged 9 and 14.

The degree of stuttering was judged on a 5-point scale by clinically experienced speech pathologists on the basis of standardized assessment sessions in which the child was to read and talk spontaneously. The behavioral changes were spontaneously reported by the children as well as their parents when interviewed by a child psychiatrist. Five children were observed to show an obvious decrease in stuttering after 2.5 months of clonidine administration. The other two children (13 and 14 years old) did not show a significant decrease in stuttering. However, all children reported improvement with respect to at least one of the following behavioral aspects: sustained attention, fine motor activity (handwriting), hyperactivity, anxiety, sleep pattern, social engagement, and school performance.

The results of this open trial were considered encouraging enough to start a double-blind crossover study to investigate systematically whether stuttering children do indeed receive any benefit from clonidine administration.

Clonidine is a centrally active compound that stimulates presynaptic α-adrenergic receptors and reduces the firing rate of cells in the adrenergic nucleus locus ceruleus. Clonidine has previously been shown to benefit children with Tourette's disorder (5) and children with attention deficit hyperactivity disorder (6). Our preliminary findings suggest that clonidine may also be a useful agent for the treatment of stuttering in children.

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## Dr. Brady Replies

SIR: I find the observations of Dr. Vink and associates of great interest. If their double-blind trial confirms their earlier study, and their results are confirmed by others, another category of pharmacologic agent will have been identified which ameliorates stuttering in some persons. Add $\alpha_2$-noradrenergic agonists to neuroleptics, calcium channel blockers, and possible cholinergic drugs. The intriguing question is, What do all these agents have in common? Alternatively, is stuttering the recognizable, symptomatic manifestation of any number of different CNS pathologies, each responsive to a different category of pharmacologic agent?

JOHN PAUL BRADY, M.D.
*Philadelphia, Pa.*

## Body Dysmorphic Disorder

SIR: The findings described by Katharine A. Phillips, M.D. (1) in her excellent review article on this interesting disorder closely parallel those I have encountered with the four patients I have seen with it in the past 20 years. Two of the four individuals I treated were men. One complained about the "repulsively aberrant" shape of his nose and the second about the "minuscule size" of his penis. The two women I have seen with this disorder both repeatedly bemoaned their fates because of the "repugnant" and "sexually shameful" size of their breasts.

Three of the four patients showed frequent mirror checking, and all four were concerned that others would mock them if they saw them in public or in a locker room type of setting. As a consequence, these three individuals suffered from considerable social withdrawal. All four patients had seen at least one plastic surgeon prior to being referred to me for treatment, and three of the four had managed to convince these doctors to perform a "cosmetic" surgical procedure on them.

In all four of these cases, there was no evidence of a thought disorder in any other area than that of the bodily preoccupation, and the most reasonable diagnosis for all four individuals seemed to be obsessive-compulsive disorder. In all four instances, the symptoms became more intense in direct proportion to the degree of intensive psychotherapeutic probing which I attempted. When the disorder became most pronounced, it was accompanied by depression in three of the four cases. This did not respond readily to tricyclic antidepressant medications in the first two patients with depression whom I saw quite some time ago. The most recent patient did show a rather rapid and positive response to fluoxetine.

It is hardly possible from my material to determine whether body dysmorphic disorder is actually a discrete syndrome or is a symptom found in a number of different nosologic entities. Only further case reports can be of help in solving this and some of the other intriguing questions which Dr. Phillips posed in her article.

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SIR: Dr. Phillips is to be commended for her thorough review of body dysmorphic disorder. This entity is characterized by constant and intense preoccupation with a body "defect" which is, in fact, quite minor or even imagined. Although Dr. Phillips mentioned briefly (p. 1141) that in a nonclinical population, up to 70% of college students expressed dissatisfaction with some aspect of their appearance, she did not make sufficiently clear that true dysmorphophobia is, so to speak, only the tip of the iceberg and that it is part of a much broader clinical phenomenon whose features, though recognizable, are not as compelling.

A majority of patients seen in intensive psychoanalytic therapy or psychoanalysis express at some point in their treatment dissatisfaction with some bodily feature. The principal differences between these patients and true dysmorphophobic patients are as follows:

1. Concern with the "defect" or physical imperfection is not a constant preoccupation, marked by intensely painful affects.
2. Reference to the "defect" is made in passing in the course of treatment and may be missed by the therapist because it is not accompanied by a striking affective display. The "defect" may not be spontaneously mentioned again by the patient for some time.
3. Reference to the "defect" usually occurs as part of a relevant associative chain. For example, an adult man mentioned that he had prominent ears in connection with material about shame and embarrassment; when he was an adolescent his ears would "light up" when he blushed with embarrassment. The therapist, incidentally, had never noticed anything unusual about the patient's ears.
4. Conscious discomfort generally is satisfactorily defended against. Mechanisms of isolation and displacement are successfully employed to avoid constant anxiety. By contrast, in true dysmorphophobia these mechanisms do not function adequately.
5. The "defect" is almost never mentioned during the initial interview and also generally not in brief or focal psychotherapies. It surfaces during the longer and less structured forms of psychotherapy.

It is difficult to find a suitable term for these somewhat ephemeral manifestations of body consciousness. A more detailed description may be found in my review articles (1, 2). Generally, however, they are underdescribed in the literature.

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PIETRO CASTELNUOVO-TEDESCO, M.D.
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## Dr. Phillips Replies

Sir: The four cases of body dysmorphic disorder described by Dr. Myers nicely and succinctly illustrate many of this disorder's common features, including the feelings of intense shame associated with the imagined physical defect, excessive mirror checking, ideas of reference, comorbid depression, social withdrawal, unnecessary cosmetic surgery, and possible response to serotonergic antidepressants. As Dr. Myers suggests, further research is needed to answer definitively the question of whether body dysmorphic disorder is a discrete syndrome or a symptom found in a variety of different nosologic entities. However, it appears that many cases of this disorder do represent a discrete syndrome. Preliminary evidence suggests that body dysmorphic disorder may respond to serotonergic medications, regardless of the "primary" or "secondary" nature of the symptoms (1), and that it may respond to treatment independently of comorbid disorders (2). It also appears that body dysmorphic disorder is often chronic, regardless of the onset or resolution of accompanying disorders, and that many patients consider it their most severe and primary problem (2). In addition, body dysmorphic disorder's precursor, dysmorphophobia, has historically been classified as a discrete disorder.

Dr. Castelnuovo-Tedesco touches on another important issue raised in my review: the similarities and differences between body dysmorphic disorder and relatively "normal" concern with appearance. Although the distinction between disorder and no disorder is inherently fuzzy for many psychiatric disorders, it may be especially so for body dysmorphic disorder, given that concern with appearance is so common.

Nonetheless, as Dr. Castelnuovo-Tedesco points out, body dysmorphic disorder can be differentiated in various ways from relatively "normal" concern with appearance, including the fact that it causes intense pain and is time-consuming. I would also add that this disorder often causes substantial impairment in functioning—individuals may drop out of school, stop working, become socially isolated or housebound, or be hospitalized because of their preoccupations. In fact, it has been proposed that, to better differentiate body dysmorphic disorder from "normal" concern with appearance, the following criterion be added to *DSM-IV*: "The preoccupation causes significant impairment in social or occupational functioning, or causes marked distress" (3).

However, I would disagree with Dr. Castelnuovo-Tedesco on one point. The literature and my experience suggest that patients with body dysmorphic disorder may make reference to their "deformity" only in passing or may never mention it to their therapist at all. While some patients vociferously complain, in a despairing fashion, about their "ugliness," others are so ashamed of and humiliated by their concerns that they keep them a secret—from family, friends, and therapists—sometimes for decades. As one patient, who took 2 years to tell me about his supposed physical defects, stated, "I didn't have the guts to talk about it." Patients may instead seek treatment for associated disorders, such as depression or anxiety. Therapists therefore need to inquire specifically about the presence of this disorder, since patients may not volunteer their preoccupations and may instead suffer silently with them for years, if not decades.

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KATHARINE A. PHILLIPS, M.D.
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## Dissociative Experiences Scale

Sir: The findings of Marlene Steinberg, M.D., and her associates (1) concerning the use of the Dissociative Experiences Scale (DES) as a screening instrument to detect patients at high risk for dissociative disorders are of interest. However, the methodology of the study is problematic in one respect. The Structured Clinical Interview for DSM-III-R Dissociative Disorders (SCID-D), administered by a clinician and used as the diagnostic standard, should have been administered *after* the patient filled out the self-report DES, not before. As it stands, the study examined the utility of the DES in detecting dissociative experiences in a population possibly sensitized to those issues by having been through a SCID-D. It is therefore difficult to generalize to other populations not so intensively interviewed. Administering the DES first would have avoided this problem.

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## Dr. Steinberg and Associates Reply

Sir: Dr. Liebowitz raises an important issue. It is possible that the administration of the SCID-D prior to the DES could have increased the patients' awareness of dissociative experiences investigated by the DES. On the other hand, it is also possible that this was not the case. Because this is an important empirical question, we have been conducting an ongoing investigation during the past year in which we have administered the SCID-D after any screening instruments have been given. We look forward to publishing further reports on these investigations.

MARLENE STEINBERG, M.D.
BRUCE ROUNSAVILLE, M.D.
DOMENIC CICCHETTI, PH.D.
*New Haven, Conn.*

## Anxiety Disorders and Parkinson's Disease

Sir: We found of great interest the article by Murray B. Stein, M.D., and colleagues (1) and the letter from Edward C. Lauterbach, M.D., and Roger C. Duvoisin, M.D. (2), who found a high prevalence of anxiety disorders in patients with Parkinson's disease. Dr. Stein and associates speculated that this high prevalence might be due to some common pathophysiologic mechanism in both disorders, and they suggested that this mechanism could be a dopaminergic deficit.

Along this line, Cash et al. (3) found that in the locus ceruleus of normal human brains there is a high dopamine/norepinephrine ratio (range, 14%), and in the locus ceruleus of nondemented patients with Parkinson's disease there is a 42% reduction in dopamine but not in norepinephrine concentrations. We believe this could be due to loss of dopamine cells in the mesencephalon that project to the locus ceruleus.

Cedarbaum and Aghajanian (4) pointed out that dopamine decreases the firing rate of the locus ceruleus. The loss of dopaminergic inhibition of the locus ceruleus could in part explain the high prevalence of anxiety disorders, especially panic attacks, in patients with Parkinson's disease. This would be consistent with Dr. Stein and associates' speculations and with recent works which find dopamine regulation of the locus ceruleus to be relevant in the pathophysiology of anxiety disorders and panic attacks in particular (5, 6).

It would be of interest to determine whether the prevalence of anxiety disorders is high only in nondemented Parkinson's disease patients. This would concur with the findings of Cash et al. that the imbalance of dopamine/norepinephrine concentration in the locus ceruleus, mentioned above, occurs only in nondemented patients, as in demented patients with Parkinson's disease there is a reduction in both dopamine and norepinephrine (this would be inconsistent with the appearance of anxiety disorders).

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LUIS CABALLERO, M.D.
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## Dr. Stein and Dr. Uhde Reply

SIR: We appreciate Dr. Iruela and colleagues' comments regarding the relationship between anxiety disorders and Parkinson's disease. They speculate that an abnormality of dopaminergic regulation of locus ceruleus firing may be a core pathophysiologic feature in these cases. They predict that only parkinsonian patients without dementia would suffer from a high rate of anxiety disorders, based on the work of Cash et al. In our study we only examined patients with Parkinson's disease who were not cognitively impaired. Consequently, we are unable to provide any data to confirm or disconfirm this very interesting hypothesis.

In addition to generating this testable hypothesis, the comments of Dr. Iruela and colleagues highlight the evolving body of research data which tentatively implicates a dopaminergic deficit in some forms of anxiety (1), perhaps especially social anxiety (2, 3). In our study, we found remarkably high rates of social phobia (which, in our opinion, could not be totally accounted for on the basis of self-consciousness regarding parkinsonian symptoms) in the patients with Parkinson's disease. We would be especially eager to have other investigators attempt to replicate this finding, inasmuch as the DSM-IV Task Force is interested in the relationship between social phobia and axis III disorders such as Parkinson's disease. We hope that the comments by Dr. Iruela and colleagues will serve as an impetus to the further study of dopaminergic function and anxiety at both the preclinical and clinical level.

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*Reprints of letters to the Editor are not available.*

## Corrections

In the article "Controlled Investigation of the Amobarbital Interview for Catatonic Mutism" by W.V. McCall, M.D., et al. (February 1992 issue, pp. 202–206), under the *Subjects* section on p. 203, the first sentence of the third paragraph should read "Each patient at the state hospital was examined by a neurologist at the time of the interview and was found free of localizing signs." On the same page, under the *Procedure* section, the fourth sentence of the first paragraph should read "A second psychiatrist (W.V.M.) conducted the interview, and a third physician administered the intravenous infusion."

In the reply by Joel Paris, M.D., and Hallie Zweig-Frank, Ph.D., to the letter "Borderline Patients' Perceptions of Their Parents" from Rex William Cowdry, M.D., and Kathleen M. O'Leary, M.S.W. (March 1992 issue, p. 427), there was a typographical error in the number of years in the next-to-last sentence of the second paragraph. The sentence should read as follows: "Our instrument, the Parental Bonding Index, is designed to measure recollections of abnormal parenting over the first 16 years of life."

# AIDS Policy:
# Guidelines for Outpatient Psychiatric Services

*This revision of the statement originally adopted in September 1988 was proposed by the Commission on AIDS.*[1] *It was approved by the Board of Trustees in December 1991.*

Psychiatrists providing outpatient psychiatric care to HIV-infected patients and those at risk are faced with several important tasks: to ensure care of the highest quality, to respect the confidentiality and rights of infected patients, and to protect others from outpatients whose behaviors could transmit HIV infection.

## PATIENT CARE

All available evidence indicates that AIDS is a disease of low transmissibility in the medical setting. Education and counseling regarding HIV transmission must be provided to psychiatrists and other medical personnel.

1. All psychiatric patients should be treated on the basis of their clinical condition; HIV infection, serologic status (e.g., HIV status), or suspicion that the patient is at risk for HIV infection should not, in and of itself, impede the delivery of appropriate medical-psychiatric treatment.

2. In therapeutic relationships, the psychiatrist should work with patients to reduce risk behavior regardless of serologic status.

3. Psychiatrists should be competent in counseling patients regarding seeking HIV serologic testing. Psychiatrists should be well informed about the need for pre- and posttest counseling. Psychiatrists should be able to distinguish anonymous and confidential testing and should know the implications and limitations of confidentiality.

4. In situations where a psychiatrist has received convincing clinical information that the patient is infected with HIV, the psychiatrist should advise and work with the patient either to obtain agreement to cease behavior that places others at risk of infection or to notify individuals who may be at continuing risk of exposure. If a patient refuses to agree to change behavior or to notify the person(s) at ongoing risk or if the psychiatrist has good reason to believe that the patient has failed to or is unable to comply with this agreement, it is ethically permissible for the psychiatrist to notify identifiable persons who the psychiatrist believes to be in danger of contracting the virus, or to arrange for public health authorities to do so.

5. Although HIV is an infection of low transmissibility in the medical setting, psychiatrists have a responsibility to reduce risk of HIV transmission from patient to patient, patient to staff, and staff to patient.

All patients and staff should be considered potentially at risk for transmitting or receiving HIV infection. A minimal standard of care should include the following:

   a. Implementation and monitoring of infection control procedures as outlined by current Centers for Disease Control standards.
   b. Appropriate management of affective, cognitive, and behavioral disturbances to ensure risk reduction for both patients and personnel.

6. AIDS education is important in the treatment of all psychiatric patients. Culturally sensitive and age-appropriate educational and supportive services for patients, families, and staff should be available. Such services would include the following:

   a. Printed educational materials readily available to patients and staff.
   b. Education regarding behaviors that place an individual at risk for HIV infection, and alternative behaviors.
   c. Evaluation of a patient's behavior for assessment of risk to self or others.
   d. Discussions of HIV testing that include indications for and consequences of such testing.

7. Psychiatrists should obtain consent to contact and communicate with the medical care providers of HIV-infected patients and to facilitate a referral if medical care is inadequate or nonexistent.

## CONFIDENTIALITY AND RIGHTS

Psychiatrists and other members of the clinical team should respect the patient's right to privacy. Disclosure of a patient's serologic status (e.g., HIV status) should be limited to those staff directly involved in the patient's care when such disclosure is appropriate for diagnosis, management, and treatment. Disclosure to other clinic or office staff is not appropriate. Psychiatrists and HIV-infected patients should appreciate the problems associated with unwarranted disclosure of serologic status. Psychiatrists should further be aware of regional legislation or statutory regulations regarding disclosure of serologic status. Patients should be made aware of clinic or office policy regarding documentation of serologic status in medical records. If clinic or office policy compels documentation of HIV serologic status in the medical record, the patient should be informed of such policy before initiating treatment.

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[1] The members of the Commission on AIDS are Marshall Forstein, M.D. (chairperson), Alexandra Beckett, M.D., Eric Bing, M.D., Robert P. Cabaj, M.D., Jacqueline Etemad, M.D., Frank Fernandez, M.D., Janice Hutchinson, M.D., Joyce Johnson, D.O., Robert Kertzner, M.D., Stuart Nichols, M.D., David Rosmarin, M.D., Simon Auster, M.D. (corresponding member), James Krajeski, M.D. (corresponding member), Andrea Moskowitz, M.D. (Board liaison), and James Nininger, M.D. (Assembly liaison).

# AIDS Policy: Guidelines for Inpatient Psychiatric Units

*This revision of the statement originally adopted in December 1987 was proposed by the Commission on AIDS.[1] It was approved by the Board of Trustees in December 1991.*

Psychiatrists providing inpatient psychiatric care to HIV-infected patients and those at risk are faced with several important tasks: to ensure care of the highest quality, to respect the confidentiality and rights of infected patients, and to protect other patients and staff from behaviors that could transmit HIV infection.

## PATIENT CARE

1. HIV-infected patients are entitled to the same standard of care as other patients. This includes rigorous diagnosis and treatment of mental disorders. In addition, psychiatrists should understand how HIV-related medical conditions may affect psychiatric diagnosis and treatment.
2. HIV serologic testing of psychiatric inpatients should be performed on a case-by-case basis when medically indicated and with informed consent. HIV serologic testing should not be performed solely for the purpose of routine screening or staff awareness.
3. In addition to treating the psychiatric disorders of HIV-infected persons, inpatient psychiatric care should also include counseling regarding risk reduction measures and education about medical treatment for HIV infection and its complications. Discharge planning should address the patient's needs for ongoing medical care. Family members and significant others should be involved in counseling and education, if appropriate.
4. Sex and needle sharing do occur in psychiatric inpatient settings. It is unacceptable to fail to protect patients from such high-risk behaviors. However, in acknowledging our limitations, we must develop strategies for safeguarding patients while they are in the hospital and for preparing them to safeguard themselves when they leave the hospital. Certain populations, such as youth, the chronically mentally ill, the developmentally disabled, and the chemically dependent, may be particularly vulnerable to unwanted sexual advances or may not be able to make free and informed choices regarding consensual sex. This issue will be addressed in full in a separate document.
5. When discharge is otherwise clinically appropriate, and if the patient represents a substantial risk of danger to others by virtue of behavior known to transmit the virus and if this danger is not related to a specific mental condition, it is inappropriate to retain the patient in the hospital solely for the purpose of quarantine or preventive detention.

## CONFIDENTIALITY AND RIGHTS

Psychiatrists and other members of the clinical team should respect the patient's right to privacy. Disclosure of a patient's serologic status (e.g., HIV status) should be limited to those staff directly involved in the patient's care when such disclosure is appropriate for diagnosis, management, and treatment. Disclosure to other hospital staff (e.g., housekeeping staff, attending physicians on other services) is not appropriate. Psychiatrists and HIV-infected patients should appreciate the problems associated with unwarranted disclosure of serologic status. Psychiatrists should further be aware of regional legislation or statutory regulations regarding disclosure of serologic status. Patients should be made aware of hospital policy regarding documentation of serologic status in medical records. If hospital policy compels documentation of HIV serologic status in the medical record, the patient should be informed of such policy before admission.

## PROTECTION OF PATIENTS AND STAFF

1. Although HIV is an infection of low transmissibility in the medical setting, psychiatrists have a responsibility to reduce risk of HIV transmission from patient to patient, patient to staff, and staff to patient.
2. All patients and staff should be considered potentially at risk for transmitting or receiving HIV infection. A minimal standard of care should include the following:
   a. Implementation and monitoring of infection control procedures as outlined by current Centers for Disease Control standards.
   b. Appropriate management of affective, cognitive, and behavioral disturbances to ensure risk reduction for both patients and personnel.
   c. Appropriate education and supportive services for patients, families, and staff.
3. If a patient known to be HIV infected engages, or threatens to engage, in behavior that places other individuals at risk, the responsible physician should assure that appropriate steps are taken to control the behavior and, if necessary, isolate and/or restrain the patient. Adequate supervision must be available to ensure that all patients, regardless of serologic status, are not able to engage in behavior likely to transmit HIV in the inpatient setting. Disclosure of a patient's HIV status to other patients is not a substitute for adequate clinical care and supervision (see APA "AIDS Policy: Confidentiality and Disclosure"—currently under review).
4. Should a health care worker or patient come into significant contact with blood or other potentially infective body fluids, the source should be approached regarding voluntary HIV serologic testing.

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[1] The members of the Commission on AIDS are Marshall Forstein, M.D. (chairperson), Alexandra Beckett, M.D., Eric Bing, M.D., Robert P. Cabaj, M.D., Jacqueline Etemad, M.D., Frank Fernandez, M.D., Janice Hutchinson, M.D., Joyce Johnson, D.O., Robert Kertzner, M.D., Stuart Nichols, M.D., David Rosmarin, M.D., Simon Auster, M.D. (corresponding member), James Krajeski, M.D. (corresponding member), Andrea Moskowitz, M.D. (Board liaison), and James Nininger, M.D. (Assembly liaison).

# APA Actions on Reproductive Rights

*This statement was proposed by the Committee on Women*[1] *of the Council on National Affairs. It was approved by the Board of Trustees in September 1991 and by the Assembly of District Branches in November 1991.*

## BACKGROUND

The APA position statement on abortion states,

> The American Psychiatric Association 1) opposes all constitutional amendments, legislation, and regulations curtailing family planning and abortion services to any segment of the population; 2) reaffirms its position that abortion is a medical procedure in which physicians should respect the patient's right to freedom of choice—psychiatrists may be called on as consultants to the patient or physician in those cases in which the patient or physician requests such consultation to expand mutual appreciation of motivation and consequences; and 3) affirms that the freedom to act to interrupt pregnancy must be considered a mental health imperative with major social and mental health implications.

It has also been shown that the children of unwanted pregnancies are at high risk for abuse, neglect, illness, and deprivation of a high quality of life. Despite such data, there are still efforts by individuals, groups, and governments to restrict family planning information, research on abortion methods, and a woman's right to have accurate information about her various reproductive options, including her choice to terminate her pregnancy.

## PROBLEM

A number of recent events threaten to erode the rights of women to freedom of choice concerning reproductive options. These include the recent Supreme Court decision resulting in a "gag rule" for information about pregnancy termination options in clinics receiving federal funds, the most recent Supreme Court appointment, and the publicity about RU-486 research.

## ACTIONS

The APA Board of Trustees pledges to immediately take the following actions congruent with the APA position statement on abortion.

1. APA will align with the AMA and other groups through appropriate lobbying efforts in Congress to prevent a veto of the recently passed legislation striking down the regulations that restrict professionals' freedom of speech in discussing therapeutic abortion as a reproductive option.
2. APA will support access to family planning services both domestically and internationally by requesting the Medical Director to write to Louis Sullivan, M.D., Secretary of the U.S. Department of Health and Human Services, and to Antonia Novello, M.D., the U.S., Surgeon General, stating APA's position on abortion and expressing our concern about the adverse effects on women and children's mental health of the "gag rule."
3. APA will become an active participant with organizations such as the American Association for the Advancement of Science, the American Pediatric Society, the Society for Pediatric Research, the American Institute of Biological Sciences, and the Cancer Patient Action Alliance in their efforts to lobby the government to permit research in North America on the efficacy and benefits of RU-486.
4. APA will continue to work vigorously at the local and national levels by having the Joint Commission on Public Affairs promulgate APA's position statement on abortion in the service of improving currently attenuated and threatened access to the full array of reproductive services. For example, APA should circulate copies of the position statement to the district branches and ask them to be active at the local level in affirming this position. APA should also actively respond to possible restrictions on women's rights to abortion by assertively stating and explaining its position.

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[1] The members of the Committee on Women are Gail E. Robinson, M.D. (chairperson), Carole J. Barry, M.D., Mindy J. Fullilove, M.D., Donna E. Stewart, M.D., Christine Y. Chang, M.D., Kathleen McKenna, M.D. (consultant), Mai-Phuong Nguyen, M.D. (APA/NIMH Fellow), and Yvonne B. Ferguson, M.D. (Assembly liaison).

# Position Statement on the Care of Pregnant and Newly Delivered Women Addicts

*This statement was proposed by the Committee on Women*[1] *of the Council on National Affairs. It was approved by the Board of Trustees in June 1991 and by the Assembly of District Branches in November 1991.*

## RATIONALE

The substance abuse epidemic, especially the use of crack cocaine and including alcohol, has resulted in tragic damage to and neglect of users and their children. This epidemic, which disproportionately affects women of color, is a social, medical, and legal crisis.

Substance abuse is a psychiatric disorder. Many of the women affected suffer from psychiatric comorbidity. Many suffer from abuse and deprivation.

Many of the children of these mothers suffer from arousal and affective regulatory problems, language disorders, and impulsive and hyperactive behavioral difficulties that require psychiatric assessment and intervention.

There has been a recent trend toward prosecution, on grounds of child abuse, of pregnant and/or postpartum women who use illegal substances, with subsequent incarceration, either in prison or in locked psychiatric units. This seriously disrupts the incipient or nascent maternal-infant bond.

In many or most geographic areas, there are few voluntary treatment facilities or far fewer beds than the number of affected women. This is unfortunate as evidence shows that during pregnancy and the 2 years postpartum women are particularly open to treatment and it is highly effective.

## ACTIONS

The APA Board of Trustees intends to take a leadership role in advocating on behalf of both these mothers and their children with departments of social services or their agencies that are legally responsible for the safety of these children. This advocacy will serve to enhance these mothers' parenting, to preserve the integrity of their families whenever possible, and to ensure the safety of their children. APA also takes the following specific positions.

1. APA opposes the criminal prosecution and incarceration of pregnant and/or newly delivered women on child abuse charges based *solely* on substance abuse. (Child abuse charges may be appropriate when a substance abuser goes on to neglect or abuse her child.)
2. APA advocates that adequate prenatal care be available to all pregnant women, including pregnant addicts, irrespective of ability to pay and without fear of punitive consequences.
3. APA urges that societal resources be directed not to punitive actions but to adequate preventive and treatment services for these women and children. APA strongly advocates the development and funding of the necessary inpatient, outpatient, and residential programs for mothers with their children. Services should address and foster the parental function, as well as the care of individual mother and child.

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[1] The members of the Committee on Women are Gail E. Robinson, M.D. (chairperson), Carole J. Barry, M.D., Mindy J. Fullilove, M.D., Donna E. Stewart, M.D., Christine Y. Chang, M.D., Kathleen McKenna, M.D. (consultant), Mai-Phuong Nguyen, M.D. (APA/NIMH Fellow), and Yvonne B. Ferguson, M.D. (Assembly liaison).

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# Position Statement on the Right to Privacy

*This statement was proposed by the Committee on Gay, Lesbian, and Bisexual Issues*[1] *of the Council on National Affairs. It was approved by the Assembly of District Branches in November 1991 and by the Board of Trustees in December 1991.*

The American Psychiatric Association supports the right to privacy in matters such as birth control, reproductive choice, and adult consensual sexual relations conducted in private, and it supports legislative, judicial, and regulatory efforts to protect and guarantee this right.

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[1] The members of the Committee on Gay, Lesbian, and Bisexual Issues are Richard A. Isay, M.D. (chairperson), Margery Sved, M.D., Rochelle L. Klinger, M.D., Robert M. Kertzner, M.D., Debbie Rene Carter, M.D., Kenneth Ashley, M.D. (APA/NIMH Fellow), and Robert P. Cabaj, M.D. (Assembly liaison and corresponding member).

THE AMERICAN JOURNAL OF PSYCHIATRY

*Special Articles*

# Philippe Pinel's "Memoir on Madness" of December 11, 1794: A Fundamental Text of Modern Psychiatry

Dora B. Weiner, Ph.D.

*Philippe Pinel's "Memoir on Madness" can now be precisely dated. It was read to the Society for Natural History in Paris on Dec. 11, 1794, soon after the fall of the Jacobin dictatorship. It is thus a* political *document, an appeal to the Revolutionary government to build asylums where the mentally ill could be decently treated. It is translated here for the first time. Philippe Pinel (1745–1826) served as "physician of the infirmaries" at Bicêtre, the public hospice for men near Paris, from 1793 to 1795. In the "Memoir on Madness" he explains his "psychologic treatment," the principles of the humane method that made him the founder of psychiatry in France. Pinel states that mental illness is often* curable. *To arrive at a diagnosis, the physician must carefully observe a patient's behavior, interview him, listen carefully, and take notes. He must understand the natural history of the disease and the precipitating event and write an accurate case history. Diagnosis and prognosis can then be made. Periodic patterns of mental illness can be helpful for therapy. Usually only one faculty is affected. Patients with delusions may be malicious or murderous. They may have to be restrained; it was Pinel's assistant, Jean Baptiste Pussin, who removed the chains from the insane men at Bicêtre Hospice in 1797 and replaced them with straitjackets. Pinel followed suit at the Salpêtrière, the public hospice for women, 3 years later. Pinel here states that one must "dominate agitated madmen while respecting human rights."*

(Am J Psychiatry 1992; 149:725–732)

The essay presented here for the first time to the English-speaking reader should be considered as a fundamental text of modern psychiatry because of its author, its contents, and the extraordinary historic circumstances under which it was first read to a Revolutionary audience in Paris. It is a classic text for psychiatry. It was recently published in French, but only now can a precise date be given for its public presentation, thus establishing its full meaning, professional impact, and political purpose (1).

The author was then a physician just short of his 50th birthday, known in Paris medical circles as the editor of the *Gazette de santé* and among natural scientists as a regular contributor to the *Journal de physique.* His M.D. degree from the University of Toulouse, awarded on Dec. 21, 1773, licensed him to practice in that town only. So he supported himself for the subsequent 20 years in Montpellier and Paris with lessons in mathematics and the translation of medical works such as

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William Cullen's *First Lines in the Practice of Physic* in 1785 (2). He also practiced a little medicine on the sly and served as consultant at the nursing home of Jacques Belhomme (1737–1824), where some mental patients attracted his attention. Meanwhile, his research interest veered toward natural history.

Pinel's systematic involvement with nature began on botanizing expeditions under the leadership of Louis Guillaume Dubernard, professor of pharmacy and chemistry at Toulouse. What a revelation the botanical gardens at Montpellier must have been when Pinel first visited them in 1774! Here the great botanist Joseph Tournefort (1656–1708) had arranged over 10,000 species in the order in which he believed the Almighty had created them. The Royal Botanical Gardens in Paris, directed by Georges Leclerc, count de Buffon (1707–1788), were a grander establishment to be sure, but no richer in plant varieties. The main difference was the large number of brilliant naturalists and *philosophes* interested in nature whom Pinel met in Paris, with whom he could interact at the Gardens as well as in salons and coffee houses, academies, and societies. A topic of lively discussion in the 1770s and 1780s was species formation—whether God had created nature once and for all times, or whether new plant or animal species might have been formed after the Flood. Pinel inclined toward the latter view: he studied animal skulls, particularly the articulation of the jaw, and found it to be adapted to the mastication of specific foodstuffs. He measured the skulls for shape and dimensions, musing about the size and functions of the brain in a search for classificatory clues.

The Paris Botanical Gardens evolved into a scientists' haven in the early 1790s when radical revolutionaries abolished most learned institutions of the old regime, perceiving them as centers of elitism and privilege. But some naturalists with good political connections convinced the Jacobins that natural history was a democratic pursuit, in contrast to science and medicine. This odd theory worked, with the result that the Botanical Gardens—now the Muséum national d'histoire naturelle—and the Society for Natural History, to which Pinel belonged, attracted a growing number of physicians such as Félix Vicq d'Azyr (1748–1794) and Jean Noël Hallé (1754–1822), who now mingled with naturalists and other scientists including Jean Baptiste de Lamarck (1744–1829), Etienne Geoffroy St. Hilaire (1772–1844), Georges Cuvier (1769–1832), and Antoine Laurent Lavoisier (1743–1794). The controversy over classification involved them all, as we learn from the minutes of the Society, some of them in Pinel's hand.

Pinel was appointed "physician of the infirmaries" at Bicêtre, the public hospice for men near Paris, on Aug. 6, 1793, and entered that forbidding fortress on Sept. 11. His attention immediately focused on the seventh ward, where 200 mentally ill men were housed. He asked for a report on the inmates and within a few days received a table with comments from the "governor," Jean Baptiste Pussin (1745–1811), the man who would become his trusted collaborator (3). In the introduction to his famous *Treatise on Insanity* of 1800, Pinel explained that he "abandoned the dogmatic tone of the physician and . . . talked repeatedly with the man who was most familiar with [the inmates'] previous state and their delirious thoughts . . . in order to ask him numerous and repeated questions . . . . " His ultimate purpose, Pinel announced, was to "enrich the medical theory of mental illness with all the insights that the empirical approach affords." At the same time he aimed at "providing practice with the general principles that it lacked" (4). A comparison of Pinel's "Memoir on Madness" with "Observations of Citizen Pussin on the Insane" shows how much the two men learned from each other (5).

While thus honing his understanding of the mentally ill, Pinel transferred his interest in natural history from the botanical garden to the mental hospital. It was not long before he measured human heads, shifting his concern from the classification of animals to a triage of patients and their division into "distinct species." He jotted down an initial, crude classification in a "General Table of the Madmen at Bicêtre Numbering about 200," which has been preserved (6).

Within a year his attention would again be diverted, this time to the classification of all diseases. His appointment to a professorship in "internal pathology" at the new Revolutionary Paris Health School led him to compose a textbook of nosology in clear and simple French. The *Philosophic Nosography* became a fundamental text for a whole generation of French medical students, as the demand for six editions from 1798 to 1818 indicates (7). He also published a second, much enlarged, edition of the *Treatise on Insanity*, and this book was translated into several European languages (8).

But during his 19 months at Bicêtre Pinel's preoccupation remained focused on pathologic human behavior, the study of what he would soon call "mental alienation." He detected in specific behaviors the signal of malfunction or abolition of one or another mental faculty. This perception derived from the observation of the patients in relation to their natural surroundings, and he combined this with the concept that diseases also have a natural history. Therefore each illness represented the intersection of a human being at a specific moment in life with a disease at a particular stage of its development. That is why Pinel meant his memoir to be a "contribution to the natural history of man." It goes without saying that this approach blurred distinctions between somatic and psychologic signs and symptoms. As clinician, author, and professor of "internal pathology" for 30 years, Pinel never concentrated on diseased limbs and organs, as would his students, for example, Xavier Bichat (1771–1802) and René Théophile Hyacinthe Laënnec (1781–1826). The hundreds of case histories in Pinel's book *Clinical Medicine* show that he always approached the patient as an integral human being (9).

It is from the minutes of the Society for Natural History that we garner new information about Pinel, for example, from 16 autograph folio pages entered when he served as secretary for the first 6 months of 1792. His appearances at the society became rare after his appointment as physician at Bicêtre. But on the first of December 1794 he announced personally that he wished to speak on the 11th—the society then met every *décadi.* The date itself is revealing, for on the fourth—Frimaire 14, Year III of the Revolutionary calendar—the government published legislation creating the new Health Schools and on Dec. 14 Pinel was named associate professor of medical physics, second in command to the famous hygienist Jean Noël Hallé. (Pinel rose to professor of "internal pathology" 6 months later.)

The inference is obvious. His sponsors in the Committee of Public Instruction and in the Paris Hospital Commission—Michel Augustin Thouret (1748–1810), Jacques Cousin (1739–1800), and Georges Cabanis (1757–1808)—thought it politic that their professorial candidate have some public exposure. Pinel seized the occasion to announce his pathbreaking innovations at Bicêtre: the long-term observation and individual management of the mentally ill, even the poorest among them, in a psychologically sensitive manner and without violence—he called this "*traitement moral.*" He stated publicly that mental illness may be curable. He explained the main categories adopted in his classificatory scheme; his concurrence in the view that mental illness usually involves specific mental faculties, not the mind as a whole; his differential diagnosis between continuous and "periodic" insanity (which he named); and the importance of heeding the signs and symptoms that signal the onset and resolution of violent attacks. These concepts, some traditional, some original, blossomed into three papers that Pinel presented to the Society of Medical Emulation and became three chapters of the *Treatise on Insanity.* It is important to point out that "*traitement moral*" meant psychologic treatment, in contrast to physical treatment, and the term should not be translated into the English "moral" with its connotation of moralizing, which the French does not convey. As for periodic insanity, it was a new concept with profound implications for therapy. If the patient was intermittently insane, then he or she was intermittently sane. Knowing this, the therapist could attempt to establish confidence and a good relationship with the sane part of the person and involve the patient in the therapeutic process. Gladys Swain has brilliantly analyzed this idea in *Le sujet de la folie,* revealing that as great a thinker as Georg Wilhelm Friedrich Hegel (1770–1830) singled out Pinel's innovative concept (10, 11).

No physician had yet written case histories as sympathetic and eloquent as the ones that Pinel read to the Society for Natural History in December 1794. We turn, for example, to the vignette of the clockmaker who believed himself seized by perpetual motion or the white-haired 70-year-old who was convinced that he was a young woman. These would soon be quoted in the whole Western literature of the nascent psychiatric specialty. By speaking of these destitute mentally ill men with understanding and respectful kindness toward each inmate, Pinel initiated a new tone, lowered fear of the insane, and facilitated a more evenhanded, democratic approach to public medicine in large hospitals. He paid tribute to Jean Baptiste Pussin, whose reliance on firm and even authoritarian behavior Pinel adopted when this seemed necessary to ensure everyone's safety. Although condemning physical mistreatment, Pinel condoned the exceptional use of threats and chains when all other means failed: for example, he cites in this memoir three patients shackled for 15, 25, and even 45 years, and he made no move at that time to eliminate the iron shackles or to replace them with straitjackets. It was Pussin who initiated these humane measures at Bicêtre in May–June of 1797, as he records in his "Observations," dated Dec. 21, 1797. Pinel followed Pussin's example 3 years later at the Salpêtrière, the public hospice for women, where he then served as physician-in-chief. Pinel recorded these crucial, humane changes in the second edition of his *Treatise* in 1809 (where he mistakenly gives the date of Pussin's initiative as 1798, instead of 1797) (p. 201 and introduction, p. xxxi). The "governor" set the example that the physician incorporated into broadly conceived reforms.

Several jibes at England for keeping her successful methods secret remind us that the two countries were then at war and that, among other things, this memoir was a political document. It also points to Pinel's awareness of his colleagues' efforts across the channel. Addressing the French government directly, Pinel presented a plan for improvements, demanding more funds and facilities, an asylum worthy of the French nation. As Jacques Postel rightly remarks, this memoir is "the matrix of the future *Treatise on Insanity*" (1, p. 233). One must not forget that these statements came from the government-appointed physician at the largest French public asylum for men, with some 4,000 inmates. The response of the Society for Natural History adds a further political dimension: "The Society voted to forward this Memoir to the Committee of Public Safety." Unfortunately, the most diligent searches in the Archives nationales have not yet turned up the manuscript (12).

The major part of this essay has been available since 1910, when René Semelaigne presented it to the French Society for the History of Medicine; Georges Bollotte republished it in *Information psychiatrique* in 1976. But not until now is there an explanation as to when and why Pinel wrote this memoir. These circumstances as well as the contents make this a pivotal text in the history of psychiatry. It expresses the fundamental new ideas and attitudes elaborated in Pinel's *Treatise on Insanity* 6 years later; it may well have been responsible for his appointment to a prominent professorship and thus have led him to compose the *Philosophic Nosography.* The date of Dec. 11, 1794, pinpoints Pinel's appearance among the reformers of mental health care in the Western world. It places him well before the opening of William Tuke's Retreat at York and makes Pinel's initial formulations exactly contemporaneous with Vincenzo Chiarugi's *Della pazzia,* thus ending

Italian claims of priority once and for all. But mainly the "Memoir on Madness" gives us what historians and psychiatrists prize: the earliest formulation of important new concepts and attitudes. Pinel, physician of the Enlightenment and the French Revolution, expresses a genuine empathy with the sufferings of ordinary men—a distraught father, a jilted lover—and points out that gifted and sensitive persons are particularly vulnerable to mental anguish. He claims for them the attention and care that the natural rights of man imply. This is a classic text because of its permanent human and humane qualities. It deserves to be known in the English-speaking world.

## "MEMOIR ON MADNESS: A CONTRIBUTION TO THE NATURAL HISTORY OF MAN," DECEMBER 11, 1794, BY PHILIPPE PINEL, M.D., PHYSICIAN OF THE INFIRMARIES, BICÊTRE HOSPICE, SEINE DEPARTMENT

When I was appointed physician of the infirmaries at Bicêtre over 1 year ago, the division for madmen attracted my special attention. I had undertaken some preliminary studies and felt the strong urge to try every means of restoring alienated reason. Thus I looked upon Bicêtre as a source of new enlightenment and instruction and a most welcome opportunity to contribute to public usefulness. But successive changes in the administration of Paris hospitals have deprived me of several facilities. I have neither baths nor showers: these were only authorized a few days ago. I have therefore restricted my activities this year to a thorough study of the true nature and varieties of madness, to the effort of obtaining for the insane everything that might improve their condition and especially to a search for fixed principles derived from nature on which to base their management and supervision, which contribute so much to the recovery of reason. I had the satisfaction of seeing 25 of 200 inmates—that is 1/8 of them—recover. I shall therefore present the result of my observations and efforts on this subject during the Year II of the Republic [Fall 1793–Fall 1794].

### I

A large gathering of madmen inspires an undefinable thoughtful tenderness when one realizes that their present state derives only from a vivid sensitivity and from psychologic qualities that we value highly. I find that truth ever more convincing and confirmed by my daily notes. Here is the father of a family whom unexpected losses have thrown into despair; here a son exhausted by work and vigils to provide for his parents' subsistence; elsewhere a passionate and sensitive young man, victim of unrequited love; there a tender husband, distracted by suspicions and the justified or false umbrage of jealousy; a young warrior thirsting for glory whose vast and ambitious projects failed, his spirit crushed by the harsh experience. Religious zeal claims its victims, as does ardent military fervor, which often expresses all the reveries and excesses of manic fanaticism. Man is most often led from the free use of reason to madness by overstepping the limits of his good qualities and of his generous and magnanimous inclinations.

The excessive sensitivity that characterizes very talented persons may become a cause for the loss of their reason: I mention this as a well-meant warning without the intention of discouraging them. Groups as diverse as investigators, artists, orators, poets, geometers, engineers, painters, and sculptors pay an almost annual price to the hospice for the insane. I have on more than one occasion stopped at the cell of a madman speaking about current affairs in the most elaborate terms and with great verve. The exalted imagination of poets also leads sometimes to madness, and I am often importuned by a confabulator who urges me to read his productions, while I see only the urgent need to subject him to treatment for madness. Recently I watched one of the most distinguished sculptors of the Pantheon die in the hospice for the insane. One of the most skillful clockmakers of Paris, infatuated with the fantasy of perpetual motion, spent a long time in the hospice but has now been returned to his family. Patriotism is pained to find among the inmates an engineer employed during the siege of the town of Condé who exhausted himself by work and sleep deprivation. There are usually some famous painters, at the moment two skilled artists named after the famous Le Sueur. I also give special care to a man versed in the most profound mathematical meditations who lost his reason because of ever-renewed fears that Vandalism visited upon true Knowledge. How many talents lost to Society and what great efforts are needed to salvage them!

Madness may be continuous during a large part of life or show long remissions, increase steadily, without interruption, or occur in regular or irregular attacks. This points to two kinds of madness: one continuous or chronic, the other intermittent or characterized by the most violent recurring symptoms.

In continuous insanity, the madman is ceaselessly preoccupied by an exclusive thought or a fixed sequence of thoughts or else led to acts of violence while his reasoning faculties appear intact. He seems dominated by a sinister tendency to harm and to destroy. This derangement of his psychologic faculties stays with him for a large part of his life, with very little change. In this hospice for the insane there is a melancholic inmate with sinister looks who has been chained for 25 years and who tries to vent his fury on anyone daring to set foot in his cell. He relents only in the presence of women, toward whom he behaves in a gentler manner. Another madman who is just as agitated and violent has been chained for 45 years, and it is only since the harsh winter of 1788 that he is calmer, or rather, advancing age has rendered him harmless. In contrast, neither the change of seasons nor the passage of time has markedly altered the condition of an Irish priest chained for 15 years: he combines a deadly inclination to harm with perfidious cunning, and his polite behavior is designed to detect opportunities for venting his fury. The insanity caused by religious fervor or a zeal for devout thoughts usually persists without interruption until the end of life. Puffed-up ambition or the mad thought of believing oneself a king or prince is just as hopeless, an almost indestructible and seductive illusion. The madman who believes he is Louis XIV and who often hands me Dispatches for the Governments of his provinces is so enchanted with his exalted power that his imagination holds on to it: he would make too great a sacrifice in stepping down from his imaginary throne.

One cannot ignore a striking analogy in nature's ways when one compares the attacks of intermittent insanity with the violent symptoms of an acute illness. It would in either case be a mistake to measure the gravity of the danger by the extent of trouble and derangement of the vital functions. In both cases a serious condition may forecast recovery, provided one practices prudent management. These bouts often depend on the seasons and should not be confused with the passing effervescence and tumultuous agitation caused by the state of the atmosphere. The fact is that in very hot weather or during thunderstorms, almost all the madmen in the hospice turn garrulous, vociferate ceaselessly, and show an agitation comparable to the violent state. But this kind of nervous excitement ends with its cause. A purely automatic imitation may also involve the madmen's limbs, imparting a temporary perturbation. Suppose a madman on the ward unexpectedly seized by an attack or, between attacks, exploding indignantly with shouts and vociferous threats against the employees or directors. It is then quite usual to see all the madmen crowd around him, share in his mental state, and participate for a few moments in this mad delirium.

The idea of madness should by no means imply a total abolition of the mental faculties. On the contrary, the disorder usually attacks only one partial faculty such as the perception of ideas, judgment, reasoning, imagination, memory, or psychologic sensitivity. A madman who died this year and who thought that he was Louis XVI was a living example of the nonconformity of ideas with the objects that occasioned them, since he saw in all persons who entered the hospice so many Pages or Guardsmen come to receive his orders. Should I give examples of errors of judgment? I found them in a rather frequent kind of madness that consists of the unfounded association of poison with food and the consequent refusal to take any nourishment. Errors of reasoning are much rarer among madmen than is commonly thought, for they derive reliable inductions from a particular sequence of ideas that preoccupies them. The white-haired 70-year-old still living at Bicêtre who believes that he is a young woman is in perfect agreement with himself when he obstinately refuses other than feminine clothing, adorns himself with care, is flattered by the polite behavior of the staff and their talk of his prospects of an approaching marriage, or when his modesty seems alarmed at the least indecent gesture. How many examples I could cite of illusions or flights of the imagination, this being one of the human faculties most susceptible to madness. A total upheaval of the rational faculty, or rather, a bizarre association of the most incongruous and incoherent ideas is quite rare, and I confine myself to citing the example of a madman whom I transferred to the infirmary a few months ago and who presents a veritable image of chaos, with the most absurd and ridiculous aberrations unconnected to any of his previous thoughts.

Madness is by no means characterized by a constant uniformity of willed physical actions or inclinations of the heart. Some madmen, possessed by a somber misanthropy, seek only solitude and live withdrawn in their cells; others remain motionless and take on a stupid expression if one speaks to them; others talk, shout, and rant day and night and appear continually agitated, but they are not to be feared unless provoked. It is distressing to see others, apparently possessed by the demon of malice, always do the opposite of what they are told in order to try the patience of the administrators, spy on the employees to trick them in mean ways or dump garbage on them, in other words, derive odious pleasure from disorder and trouble. Another much more dangerous madness seems connected with a blind rage and a kind of destructive instinct that impels to tear everything reachable to pieces and inspires the most bizarre cruelties, as some unfortunate madmen confess after their attacks subside. How often delirious fury is the product of the mystical dreams of fanaticism! One of the madmen who must be kept tightly locked up is subject to visions at night, and during these ravishing ecstasies he believes that an order from heaven commands him to bestow the Baptism of Blood and merciless immolation upon all those whose happiness in the next life he craves. How much supervision such madness demands! In the horrible derangement of his reason this wretch plunged a dagger into the hearts of his own children.

I have tried to understand how attacks of madness usually begin and have been surprised by the diversity of signs that foretell an approaching explosion of manic delirium in a variety of madmen. Sometimes there are futile excesses of fervid joy and immoderate bursts of laughter, at other times a somber taciturnity or extreme anxieties and groundless tears; a readier anger, a livelier glance, or brusque replies often lead me to predict an approaching attack and the urgent need to use coercive measures. But what seems to me likely to frustrate all human prudence is that sometimes the attack occurs with lightning speed. The eyes begin to glint, the face turns fiery, all muscles tense up violently and acquire extreme strength while the madman's single wish seems to be to tear and to destroy. What a contrast when one compares this delirious fury with the raptures of a man rendered mad by love who, the day before his attack, confided to me a dream designed to make his lifelong happiness: his love had appeared to him with features of the most ravishing beauty, and he believed that she promised soon to unite her destiny to his. I have never heard love spoken of with such ardor.

The ways of nature are no less admirable in the termination of attacks of madness than in the critical resolution of other illnesses and the gradual recovery of health. These attacks sometimes end in a kind of progression, and the madmen who had remained for a long time in a turbulent agitation or who tore everything become calmer; but they still feel troubled, their thoughts are disordered, and they themselves know that they are not sufficiently in control of themselves to be responsible for their willed behavior; each day the movements and actions that impelled them beyond the bounds of reason grow more temperate and all the mental faculties recover their rights; some of them indicate the exact moment when one can give them their freedom within the hospice, while others demand it too soon, when it would be very dangerous to turn them loose.

One can observe at Bicêtre a different outcome of madmen's attacks that requires great vigilance from the staff because it demands the most active intervention. This termination is quite abrupt and succeeded by a certain atony, a state of dejection and cold when one must warm the madman and even cover him with three or four woolen blankets to prevent his demise. The remission of maniacal delirium is most frequent in fall and early winter; if this sudden change occurs at night it can become fatal for lack of help; this happens every year, whatever precautions one may take.

To consider madness as a usually incurable illness is to assert a vague proposition that is constantly refuted by the most authentic facts. An understanding of the varieties of madness teaches one to identify the almost certainly curable cases, the doubtful ones, those where relapses are to be feared, and those without any hope of cure. If a mature man has a strong constitution, if the cause of his madness is a violent passion and the attacks recur periodically, then reason eventually regains its rights provided the madman is guided wisely and pursues work or a hobby with regularity. But what are the prospects of insanity that is hereditary or that derives from an organic flaw? Sometimes the reiterated attacks degenerate into dementia or lead slowly to the tomb. Two kinds of madness seem, more than any other, made to last a lifetime: the first springs from puffed-up self-importance, making believe that one is a prince or a divinity; the other derives from the derangements and frenzies of fanaticism. What to do for a madman grown old in the belief that he is Louis XVI who, confusing times and places, wishes me to attend him at court and thinks that he is alternately at Bicêtre, in Paris, or in Rome? But nothing is more atrocious and savage than the somber dreams and fanatical madness of an atrabilious worshiper. I have already mentioned a madman who became the executioner of his own children, seeking only to dispense a Blood Baptism that brings eternal bliss. Recently the director of the hospice was attacked by one of these pious visionaries while he was making his rounds. The madman seized him by the hair from behind, hit him repeatedly with the back of a Bible till he lost consciousness, and would unquestionably have beaten him to death had the employees not come to the rescue. When questioned a few moments later about the motive that had compelled him to commit this furious act, the madman coolly cited examples from the Bible and added that, moreover, he should be considered another Maccabaeus.

## II

The hospice for madmen at Bicêtre was considered under the old régime as no more than a place of sequestration and imprisonment for a class of dangerous men who needed to be segregated from Society. It was deemed sufficient to subject them first to a rough treatment at the Hôtel-Dieu consisting of bleedings, baths, and showers. They were then abandoned to the incompetence of a callous director and to the cold brutality of servants who opposed a premeditated force of their own to impetuous acts of a blind and seemingly automatic violence. No one paid heed to the only means of restoring deranged reason firmly; I mean the art of studying the tastes and inclinations of the various madmen in order to guide them in a contrary direction, and the even more difficult art of combining affability with firmness in a well-timed manner, distracting the exclusive thoughts that preoccupy them, using only innocent repressive means, never blows or harsh treatment: these serve only to exasperate madness and often render it incurable.

It is true that a person who seeks to acquire the right ideas and fixed principles about the psychologic treatment of madness hardly knows where to turn. Medical treatises offer only general views, and in specialized treatises one finds only isolated observations irrelevant for a large group of maniacs. Travelers have not yet brought us specific enlightenment in their reports about various European institutions of this kind. The rights of man are too little respected in Germany to make the study of their ways of handling the insane in public establishments worthwhile. Spain has taken only a few steps toward this great goal, as I showed a few years ago in a periodic publication: the inmates of a public asylum dedicated to their custody are managed with the greatest gentleness and assigned to regular work which has served to cure most of them. But it is mainly England one must envy for the artful wisdom of managing a large group of madmen and effecting the most unexpected cures. Why does that haughty and self-righteous nation spoil such a great gift to humanity by keeping a mysterious silence and guiltily casting a veil over its skill to restore distracted reason? The English proudly display the majestic sight and the internal arrangements of the asylums that Philosophy has dedicated to the unfortunate insane. But they keep the art of managing the insane a deep secret which they apparently want to control and keep from other peoples. I have therefore been restricted this first year to the slim resources of the preliminary studies I had done and to the observations I was making daily; I have carefully examined and compared the several varieties of insanity to deduce firm rules for managing all of them. I summoned new courage for the endless fight against all kinds of obstacles, be they unsuitable lodgings or the kind of neglect from which madmen still suffer because of inveterate prejudices. I shall now indicate how their lives have been improved, until we can do better still.

I asked that the registers be used to establish an exact count of the numbers of deaths in the hospice for the insane during the years immediately preceding the Revolution. I must say that there is no more convincing evidence of the flagrant neglect to which the old regime abandoned this part of suffering humanity. Of 110 madmen admitted to the hospice during the year 1784, 57, i.e., more than one-half, died. The proportion was even worse in 1788 when 95 of 151 died, a frightening result in a group of men who are usually full of life. In contrast, during this past year, I only lost 28 of 200—and if one were to count only those who died of an illness, this would mean deducting eight who succumbed a few days after their arrival because of the violent treatment administered at the Hôtel-Dieu and four who died during epileptic fits. Among the causes that exerted such a fatal influence on the lives of the insane at Bicêtre under the old régime, one must count the lack of food, since the daily ration of bread was only one and one-half lb, with an ounce or so of a carelessly prepared dish. This ration was distributed in the morning, or rather, it was instantly devoured and the rest of the time was spent in a ravenous delirium. This only served to exacerbate their madness and caused most of them to die of exhaustion. In 1792 the hospital administration hurried to do away with this unnatural outrage, and for approximately 2 years the daily ration of bread has been raised to 2 lb, while care was taken to distribute part of it in the morning and part at night. That has stopped all complaints about the dearth of food.

True friends of humanity should also learn of the attentive empathy that the directors of the hospice for the insane have displayed in order to implement the government's wishes. One rarely sees such untiring devotion combined with resourcefulness, industry, and wise economy. To watch with scrupulous care that no foodstuffs be spoiled, to keep some reserves for difficult days and thus compensate for the unevenness of the supplies, always to serve succulent and tasty soup, as good, I daresay, as any citizen may desire, to make up for the shortages of lean days by setting aside soup bones from previous days and skillfully extracting their gelatin, intelligently to regulate the heat at which the meat is cooked by raising it first very high and then keeping it moderate for several hours, to find ingredients for two meals a day when the rest of the institution gets only one, in a word, to bring the small attentions and constant care of domestic economy to a large establishment—such is the arduous and touching task accomplished daily and modestly by the director of the hospice for the insane and his esteemed wife, in the midst of all kinds of vexations and obstacles: I present the summary of a conduct that I could document more fully, with details pried out with some insistence.

The true principles of managing the insane in a psychologically sensitive manner are also well understood at Bicêtre. I mean a kind of supervision adapted to the nature of their madness, the prevention of dangerous consequences of their impetuous outbursts without any mistreatment, a timely deprivation of liberty, or permission to move about freely within the hospice. If a madman suddenly experiences an unexpected attack and arms himself with a log, a stick, or a rock, the director—always mindful of his maxim to control the insane without ever permitting that they be hurt—would present himself in the most determined and threatening manner but without carrying any kind of weapon, so as to avoid additional vexation. He speaks with a thundering voice and walks closer toward the maniac in order to catch his eye. At the same time the servants converge on him at a given signal, from behind or sideways, each seizing one of the madman's limbs, an arm, a thigh, or a leg. Thus they carry him to his cell while thwarting his efforts and chain him if he is very dangerous or merely lock him up. That is how one dominates agitated madmen while respecting human rights. The employees are expressly forbidden to retaliate even if they are hit, but they must use force and cunning to avoid this. This is another point that I can guarantee and that I have verified several times because malevolence has ceaselessly spread rumors to the contrary.

One of the fundamental principles of the conduct one must adopt toward the insane is an intelligent mixture of affability and firmness. When they are obstinate one must sound totally superior and unshakable so as to convince them to bow to the will of the directors. But one must avoid any unnecessary constraints and use only enough force to restrain them. In order to avoid vague precepts I shall cite some facts, and I could add many more.

A soldier becomes insane and is sent to the hospice. Obsessed with the thought of his imminent departure, he obstinately refuses to go to bed in the evening or even to enter his cell, and he threatens the servants. When repeated entreaties and all other expedients prove useless, the director finds it necessary to take urgent measures. Assuming the most firm and imposing tone and surrounded by the employees, he adds threats to these terrifying preparations and has the man tied down. The madman tears everything to pieces during the night and turns so violent that recourse to chains becomes necessary. He is thus given time to expend his mad fury, and they check every day to see if he is calming down. On the eighth day, during the director's rounds, he appears submissive, kisses his hand, and says, "You promised to set me free if I was calm; well, I call on you to keep your word." The other responds in the friendliest and most fraternal manner and sets the madman free, first in his cell and then within the hospice.

Another man, dominated by religious prejudices and appalled by the abolition of the Catholic religion in France, is sent to the hospice with all the symptoms of totally alienated reason. He remains for almost 3 months in a state of somber taciturnity and hardly leaves his cell. Solitude excites his imagination, and he is ceaselessly terrorized by torments concerning the next life. Thinking about the mortifications of the saints' penitential lives, he obstinately refuses any kind of food and appears close to death. All admonitions, all enticements are in vain; he even rejects a little succulent bouillon and brushes away the straw so as to sleep on the bare floor. The director concluded that the only way to save the man is to terrorize him so as to change the direction of his sinister thoughts. He addresses him with a thundering voice, assembles all the staff, and threatens him with the harshest measures. Disconcerted and intimidated by this firm tone, the madman resolves to take nourishment and accept a softer bed than the bare floor. Sleep gradually returns, he regains strength, and escapes certain death. After recovering his reason, he admitted that he owed his cure to the measures taken to confront his derangement. He described the cruel hesitations he felt during more than 24 hours and the kind of inner struggle he experienced between the resolve to die from total abstinence and the harsh measures he faced if he refused to eat. This terror finally won out and allowed him to take substantial food, and from then on calm and sleep prepared the return of his strength.

Thus one of the major principles of the psychologic management of the insane is to break their will in a skillfully timed manner without causing wounds or imposing hard labor. Rather, a formidable show of terror should convince them that they are not free to pursue their impetuous willfulness and that their only choice is to submit. If a madman ruled by his wild extravagance sees only two or three employees advance toward him, he senses his superior strength. He will attack, wound, and crush them, and this kind of triumph will only heighten his delirium. If, on the contrary, he sees a large number of employees converge on him, he foresees a strikingly uneven contest. His agitation appears disarmed by the idea of his impotence, he will submit without resistance and grow more quiet and calm. Great skill is required to retain the insane locked in their cells only for the necessary length of time and only while they are capable of extreme acts of violence. The general rule in well-run hospices is to watch all phases of their attacks closely, anticipate their termination, and, generally speaking, grant as much freedom as possible to those madmen who content themselves with mere gesticulations, loud declamations, and acts of extravagance that hurt no one. To lock up this kind of madman on the pretext of maintaining order means to impose needless constraints that provoke his rebellion and violence and render his madness more inveterate and often incurable.

This summary review of my observations on the insane at Bicêtre indicates that we are well on our way toward the great principles of their management of which England does not hold the exclusive secret. My dedication to improving the fate of these unfortunates and enabling a large number to return to Society has been spurred by various obstacles and hurdles that hoary prejudice has raised. I wish to acknowledge the humane intelligence of the hospice's director who has assisted me. But how limited my means have been because of the unsuitable and restricted space, the impossibility of dividing the insane into general classes, the unrealized although long-held project of therapeutic baths and showers, the idleness of the inmates, and the lack of some manual labor to provide useful distraction from their somber thoughts. The Commission on Public Aid is beginning to turn its attention toward this important matter of public usefulness. But it is the Legislative Body itself that should endow a public asylum for the insane with the well-planned grand design that this nation requires. May it create magnificent establishments like those that Philosophy has erected in another country. Renouncing sumptuous ostentation that strikes the senses with vain splendor, this institution should reflect a well-ordered wisdom corresponding to the varied needs of the insane and proclaim from afar the respect due to distress and misfortune.

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# Psychotic (Delusional) Major Depression: Should It Be Included as a Distinct Syndrome in *DSM-IV*?

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*To review data supporting or not supporting the designation of unipolar psychotic major depression as a distinct syndrome in* DSM-IV, *the authors used computerized literature searches to identify reports of studies that have directly compared the characteristics, biology, familial transmission, course/outcome, and response to treatment of psychotic and nonpsychotic major depression. The review showed that statistically significant differences between the two types of depression have been found on each of these dimensions. There are greater guilt feelings and psychomotor disturbance, among other features, in psychotic depression. Studies have found significant differences between patients with psychotic and nonpsychotic depression in glucocorticoid activity, dopamine β-hydroxylase activity, levels of dopamine and serotonin metabolites, sleep measures, and ventricle-to-brain ratios. Family studies show higher rates of bipolar disorder in first-degree relatives of probands with psychotic major depression than of probands with nonpsychotic major depression. Greater morbidity and residual impairment have also been reported in patients with psychotic major depression, and they respond more poorly to placebo and to tricyclic antidepressants. Differences between patients with psychotic and nonpsychotic major depression on many of these measures were not due to differences in severity or endogenicity. Since the data indicate that psychotic and nonpsychotic major depression can be separated, the frequency with which the diagnosis of psychotic major depression is missed and its unique course and response to treatment point to the practical importance of a separate diagnosis for this disorder. However, further studies are needed to resolve important methodological issues and to develop an optimal set of operational criteria.*

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In recent years, considerable attention has been paid to psychotic or delusional depression as a distinct subtype of major depression. This disorder is quite common, representing some 25% of consecutively admitted depressed patients (1). In *DSM-III-R*, it is generally referred to as major depression with psychotic features. Data from studies on clinical signs and symptoms, biology, familial transmission, course of illness, and response to treatment suggest that delusional depression now comes close to meeting the requirements for designation as a distinct syndrome (2). In this article we review data both for and against such designation and propose that there are sufficient data and clinical reasons to include major depression with psychotic features as a distinct depressive syndrome in *DSM-IV*.

## HISTORY

Delusional or psychotic depression is a severe form of mood disorder characterized by delusions or hallucinations. The view that delusional depression is a distinct disorder has largely emerged during the era of psychopharmacology (3), and the renewed interest in this disorder rests heavily on observations made by Glassman and colleagues in their classic studies of plasma imipramine levels. The history of this syndrome has been reviewed in detail by Kantor and Glassman (3), as well as by our group (4). The significance of psychotic symptoms as predictors of outcome was explored in early studies, before the introduction of ECT. In these studies, patients with what today would be called psychotic major depression often did more poorly than

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their counterparts with nonpsychotic major depression, but the presence of delusions was by itself "not a clear predictor of outcome" (3). Patients with delusions without prominent mood symptoms, however, generally had poor outcomes.

After the introduction of ECT, interest in psychotic depression waned considerably when a number of early studies (in the 1950s and 1960s) reported that delusions predicted neither good nor poor response to ECT (3). Patients with psychotic major depression and patients with nonpsychotic major depression both responded well (about an 80% response rate) to this powerful treatment (3). (Several later studies, however, questioned these earlier findings, as we discuss later in this article.) The introduction of tricyclic antidepressants led to renewed interest in psychotic depression, as it did with other disorders, such as panic. However, in contrast to panic disorder or agoraphobia with panic attacks, which were noted to be highly responsive to imipramine, psychotic depression was, in a sense, reborn as a syndrome because it responded unexpectedly poorly to tricyclic antidepressants. This lack of response has led to numerous recent studies on clinical characteristics, biological measures, course, and familial history, many of which have argued that psychotic depression is a distinct subtype of depression and should be designated as such.

There has, however, been a longstanding debate about whether psychotic depression is indeed a distinct syndrome or merely represents a severe subtype of depression. In the European literature, "psychotic depression" generally has been used to indicate a syndrome characterized by pronounced neurovegetative signs and symptoms, with or without a thought disorder. This approach was carried over into *DSM-II* (1968), in which patients with psychotic depressive reactions were those who demonstrated severe depressive episodes in response to one or more identifiable stressors. Delusions or hallucinations were not required for fulfilling the criteria for this diagnosis. In *DSM-III* (1980) and *DSM-III-R* (1987) the dimensional qualifier "with psychotic features," as part of the fifth-digit severity code, denotes a thought disorder (i.e., the presence of hallucinations or delusions) that primarily reflects the severity of the depressive disorder rather than a distinct characteristic. However, data reviewed in this article strongly suggest a predictive validity for psychotic major depression that is more consistent with considering it as a categorical entity than as defined merely by being positioned at one end of a severity dimension. Moreover, the finding that psychotic major depression, unlike nonpsychotic major depression, does not respond particularly well to tricyclic antidepressants, but does respond to other treatment approaches, underscores the importance of careful assessment of this disorder.

We reviewed all available English-language studies on delusional (psychotic) major depression, using computerized searches of *Index Medicus* (MEDLINE) to help identify studies. Emphasis is placed on studies that directly compared samples of delusional and nondelusional patients with major depression. Tables identifying the diagnostic instruments, the diagnoses of the subjects, and the specific findings in the studies discussed in text are available from the first author on request.

## CHARACTERISTICS

The hallmark feature separating patients with psychotic major depression from those with nonpsychotic major depression is the occurrence of delusions or hallucinations in the former. Delusions can be classified broadly as guilty, paranoid, or somatic. Hallucinations are divided into auditory, visual, and somatic types. Generally, delusions are viewed as mood-congruent if they reflect lowered mood and/or underlying nihilistic, overly self-deprecatory, or guilty beliefs.

Psychotic depressions are often severe in nature, with patients demonstrating relatively high total scores on the Hamilton Rating Scale for Depression (5, 6)—often significantly higher than those of comparison groups with nonpsychotic major depression (1, 6–9). Although these observations could be interpreted as supporting the notion that psychotic depression is merely a more severe variant of depression, a number of investigators have argued that psychotic depression is a separate disorder. Studies of depression have identified patients with nonpsychotic major depression who have total Hamilton depression scores in the range seen among patients with psychotic major depression (9). Thus, the development of delusions must rest with risk factors or biological processes other than severity of depression. Moreover, in studies reporting greater overall severity of illness in patients with psychotic major depression, these patients do not demonstrate greater severity on all symptoms. Rather, differences between patients with psychotic and nonpsychotic major depression appear to occur primarily in particular symptoms or symptom clusters. For example, our group (10) reported that patients with psychotic major depression had significantly higher total Hamilton depression scores than patients with nonpsychotic major depression ($p=0.005$). This was primarily because the patients with psychotic major depression had significantly greater Hamilton depression scale factor scores for retardation ($p=0.01$) and cognitive disturbance ($p=0.005$). The Hamilton depression scale factor scores for anxiety/somatization, weight, diurnal variation, and sleep disturbance were not significantly different between the patients with psychotic and nonpsychotic major depression. On the Brief Psychiatric Rating Scale, the patients with psychotic major depression had a higher mean total score than the patients with nonpsychotic major depression ($p<0.001$) and higher factor scores for thinking disturbance ($p=0.02$), withdrawal/retardation ($p=0.02$), and hostility/suspiciousness ($p=0.009$). The two groups did not differ on the factor score for anxiety/depression.

In regard to specific symptoms, patients with psychotic major depression demonstrate significantly more severe or more common psychomotor disturbances (retardation or agitation) than do patients with nonpsychotic major depression (1, 6, 8, 9, 11, 12). Some studies (8, 11, 12) have reported greater agitation in psychotic major depression, while others (9) have reported greater retardation. At least two studies (6, 12) have reported both greater agitation and greater retardation. Only one (retrospective) study (13) failed to find significant differences in either retardation or agitation. Greater agitation or retardation in psychotic major depression does not appear to be due to increased severity. Glassman and Roose (9) reported that when patients with psychotic and nonpsychotic major depression were matched for total Hamilton depression scores, the patients with psychotic major depression still had significantly greater psychomotor retardation or agitation scores. Similar data were reported by Lykouras et al. (6). Several investigators (1, 6, 8, 9, 12) have also reported significantly greater feelings of guilt among patients with psychotic depression than among those with nonpsychotic major depression, but at least one study (14) failed to confirm this finding.

A number of other symptoms have been reported to be more pronounced in psychotic than in nonpsychotic major depression: depressed mood (1, 6, 9), paranoid symptoms (6, 8), hopelessness (8), hypochondriasis (1, 9), anxiety (9, 12), early insomnia (6, 8), and middle insomnia (6). However, the data supporting the idea that each of these is more pronounced in psychotic major depression are less robust and less consistent than are the data in support of greater psychomotor disturbance or guilt. Lykouras et al. (6) reported several differences between patients with psychotic and nonpsychotic major depression on specific symptoms (e.g., insomnia). However, after overall severity was covaried out, only depressed mood, psychomotor retardation, and paranoid symptoms remained significantly greater in patients with psychotic major depression.

Risk of suicide has been reported to be greater among hospitalized patients with psychotic major depression than among their counterparts with nonpsychotic major depression (15), and suicidal ideation has also been reported to be significantly greater among patients with psychotic major depression (7). However, other studies that compared the two groups on suicidal ideation or suicide attempts failed to find statistically significant differences between them (1, 8, 9, 11, 12, 14). These data suggest that most somatic depressive symptoms and suicidal ideation/behavior cannot be used to separate consistently patients with psychotic and nonpsychotic major depression, but that psychomotor disturbance, guilt, and psychotic symptoms do appear to separate these two groups of depressed patients.

Although psychomotor agitation and guilt appear to help separate psychotic from nonpsychotic major depression even after covarying out for overall severity, one may argue that these symptoms are merely separating patients with endogenous or melancholic major depression from their counterparts with the nonendogenous type. Although few studies have specifically examined an "endogenous" dimension separately from that of severity, it could be argued that a high proportion of severely ill, hospitalized patients with nonpsychotic major depression would also meet criteria for endogenous depression, and that these various symptoms are in fact separating psychotic major endogenous depression from nonpsychotic major endogenous depression. Still, without applying specific criteria for endogenous depression to define the nonpsychotic sample, this question is moot.

Recently, Parker et al. (16) reported on differences in symptoms between delusional and nondelusional patients, all of whom met both the *DSM-III* criteria for melancholia and the Research Diagnostic Criteria (RDC) for definite endogenous syndromes. In contrast to patients with endogenous nonpsychotic major depression, patients with endogenous psychotic major depression demonstrated significantly more frequent psychomotor disturbance, an absence of diurnal variation in mood, fixed depressive thought content, and constipation. The authors used latent class analyses and reported that psychotic features (i.e., hallucinations or delusions) were sufficient but not necessary to characterize individual patients as being "psychotic." These data suggest that psychosis is a separate dimension from endogenicity and that psychomotor disturbances do not merely separate patients with endogenous and nonendogenous disorders.

Cognitive impairment, measured objectively/quantitatively, has been less well studied than have specific symptom characteristics. We reported (17) that patients with psychotic major depression demonstrated greater impairment on neuropsychological testing than did patients with nonpsychotic major depression when severity, as measured by total Hamilton depression score, was partialed out. We hypothesized that cognitive deficits in psychotic (and in some nonpsychotic) depressed patients reflect significantly increased cortisol activity. Neuropsychological performance may provide greater specificity in separating patients with psychotic major depression from those with nonpsychotic major depression than do specific symptoms.

The studies we have described frequently compared clinical populations in tertiary care or academic settings, and in several, the study groups were identified retrospectively. Such approaches have a number of limitations, particularly potential selection bias toward patients who are more refractory to treatment or more severely ill. The Epidemiological Catchment Area study (18) recently reported that patients with psychotic major depression did not have more symptoms overall than did patients with nonpsychotic major depression, nor did the two groups differ in symptom patterns other than the presence of a thought disorder. (Specific depression rating scales were not used in that study, however.) Patients with psychotic major depression did differ significantly from patients with nonpsychotic major depression in demonstrating greater morbidity at 1 year, including more frequent suicide attempts, (see section on Course and Outcome for further discussion).

## FINDINGS IN BIOLOGICAL STUDIES

### *Studies of HPA Axis Activity*

There is now abundant evidence for specific abnormalities in patients with psychotic major depression on measures of hypothalamic-pituitary-adrenal (HPA) axis activity. Many centers have reported that patients with psychotic major depression are among those with the highest rates of nonsuppression of cortisol on the dexamethasone suppression test (DST) and/or that patients with psychotic major depression have markedly elevated postdexamethasone cortisol levels (19–29), although not all studies are in agreement (1, 7, 30, 31). Significant differences between patients with psychotic and nonpsychotic major depression have been observed on 24-hour measures of urinary free cortisol (32). Although patients with other affective psychoses such as mania show high nonsuppression rates (33), patients with nonaffective psychoses such as schizophrenia do not (24, 33).

The elevated cortisol levels after dexamethasone administration in patients with psychotic major depression are not merely due to greater severity of depressive illness or to the presence of endogenous symptoms. For example, Evans et al. (26) did not find significant differences in the rates of postdexamethasone nonsuppression between patients with nonpsychotic major depression with melancholia and patients with nonpsychotic major depression without melancholia. The two groups also did not differ on mean postdexamethasone cortisol levels, yet both groups had significantly lower mean postdexamethasone cortisol levels than did patients with psychotic major depression. Rihmer et al. (29) reported significantly higher rates of nonsuppression on the DST among psychotic endogenously depressed inpatients than among their nonpsychotic counterparts. Furthermore, Brown et al. (34) used a stepwise multiple regression analysis to examine the effects of severity, agitation, delusions, melancholic subtype, age, and weight loss on postdexamethasone cortisol levels in 93 patients with unipolar major depression. They reported that agitation predicted 22%, melancholia predicted 27%, and the presence of delusions predicted 34% of the variance in morning postdexamethasone cortisol levels. Severity of illness, age, and weight loss added no further significant predictive value and did not affect cortisol levels when examined separately from the other variables.

In summary, the vast majority of studies point to significantly greater HPA axis activity in psychotic major depression than in nonpsychotic major depression, although not all studies agree. Specific differences in patient samples (e.g., the relative proportions of unipolar and bipolar patients [1, 27] or drug-free status) could help account for the lack of consistency. The literature does not support the notion that the greater HPA activity seen in patients with psychotic major depression is merely the result of greater severity of depression, the presence of endogenous features, or the psychosis per se but, rather, is related to the interaction between the affective disorder and the psychosis. Our group (35) has hypothesized that the development of delusions in depressed patients is due to the effects of hypercortisolemia on dopaminergic systems, since glucocorticoids increase levels of dopamine in human plasma (36) and rat brain (37) and levels of homovanillic acid (HVA) in rat brain (38) as well as human CSF (39).

### *Studies of Dopaminergic Activity*

Several studies have demonstrated that in psychotic major depression there is an activation of the dopaminergic system which is not seen in nonpsychotic major depression. Patients with psychotic major depression demonstrated significantly higher levels of unconjugated plasma dopamine both before and after administration of dexamethasone (40). Studies measuring the dopamine metabolite HVA have also reported higher levels in patients with psychotic major depression. Sweeney et al. (41) reported that the probenecid-induced accumulation of HVA in CSF was higher in psychotic major depression than in nonpsychotic major depression. Furthermore, Aberg-Wistedt et al. (42) reported that patients with psychotic major depression had significantly higher concentrations of HVA in CSF than did patients with nonpsychotic major depression. Higher CSF levels of 5-hydroxyindoleacetic acid (5-HIAA) were also found in the patients with psychotic major depression (see section on Measures of Serotonergic Function).

Studies of plasma HVA also indicate that patients with psychotic major depression have greater activation of dopaminergic systems than do patients with nonpsychotic major depression. Devanand et al. (43) reported that plasma HVA levels were significantly higher in women with psychotic major depression than in women with nonpsychotic major depression. Mazure et al. (44) reported that plasma HVA levels were significantly higher in patients with psychotic major depression than in melancholic patients with nonpsychotic major depression, who in turn had higher levels than nonmelancholic patients with nonpsychotic major depression. Finally, Wolkowitz et al. (45, 46) demonstrated a trend toward relative blunting of the plasma HVA response to dexamethasone in patients with psychotic major depression compared to patients with nonpsychotic major depression. One study (47) reported no baseline differences in urinary levels of HVA in patients with psychotic versus nonpsychotic major depression. Overall, the data indicate that psychotic major depression can be distinguished biologically from nonpsychotic major depression on measures of dopaminergic activity. Although studies have generally emphasized the possible role of severity rather than that of endogenicity, the data of Mazure et al. (44) suggested that elevated plasma HVA levels in psychotic major depression are not due to the presence of endogenous features.

### *Enzyme Studies*

There has been growing evidence that certain biochemical enzyme abnormalities may be specific to psychotic major depression. Previous studies have shown that patients with unipolar psychotic major depression have lower serum dopamine β-hydroxylase activity (48, 49) and patients with unipolar nonpsychotic major depression have higher dopamine β-hydroxylase activity (49, 50) than do healthy control subjects. The low levels of serum dopamine β-hydroxylase activity in patients with unipolar psychotic major depression have been hypothesized to be a potential marker of relative risk for developing pronounced increases in dopamine levels when there is chronic elevation of cortisol levels (35).

### *CT Scans*

Several studies have reported differences on CT scans between patients with psychotic major depression and those with nonpsychotic major depression. Targum et al. (51) studied 38 melancholic depressed inpatients (unipolar and bipolar) and found that the mean ventricle-to-brain ratio (VBR) of the patients with psychotic major depression was greater (although not significantly so) than that of the patients with nonpsychotic major depression and that of comparison subjects with neurological disorders. Five (25%) of the 20 patients with psychotic major depression had VBRs greater than two standard deviations from the mean of the 26 subjects with neurological disorders, whereas none of the 18 patients with nonpsychotic major depression did. Luchins and Meltzer (52) examined VBRs in 18 depressed patients. Five (56%) of the nine patients with psychotic major depression, but only one (11%) of the nine with nonpsychotic major depression, had VBRs one standard deviation outside the control mean ($p<0.05$, Fisher's exact test). However, there was no difference in mean VBR between groups. Subsequently, Schlegel and Kretzschmar (53) reported that patients with psychotic major depression had significantly greater mean VBRs than did control subjects, whereas patients with nonpsychotic major depression did not.

We have reported (17) on VBRs in a sample of delusional and nondelusional unipolar depressed patients. Statistically significant differences between the patients with psychotic major depression and those with nonpsychotic major depression were observed in VBRs as well as in ratings of inferior parietal atrophy. The patients with unipolar psychotic major depression had significantly greater mean anterior pole and cella media VBRs and more left and right inferior parietal brain atrophy than did their counterparts with unipolar nonpsychotic major depression. The enlarged VBRs and greater inferior parietal brain atrophy in the patients with unipolar psychotic major depression were correlated with poorer performance on neuropsychological testing. Interestingly, the enlarged VBRs seen in patients with unipolar psychotic major depression were also associated with higher levels of plasma cortisol in this study (17) as well as others (54). The possible effects of endogenous symptoms generally have not been explored in these studies. Still, the data overall do suggest an association in patients with unipolar major depression between symptoms of psychosis and greater VBRs. This is in contrast to psychotic schizophrenic patients, in whom positive symptoms (delusions and hallucinations) have been associated with smaller ventricles (55, 56).

### *EEG Sleep Profiles*

Comparisons of EEG sleep profiles of patients with psychotic major depression and those with nonpsychotic major depression have also indicated differences between the two groups. Patients with psychotic major depression exhibit significantly diminished slow wave sleep, poorer sleep efficiency, and a reduced percentage of REM sleep time in comparison to patients with nonpsychotic major depression (57–60). However, these findings may have reflected differences in age, severity, and agitation between the two groups (61). In a study that specifically controlled for the effects of age, severity, agitation, and other clinical characteristics (62), patients with psychotic major depression were found to have greater wakefulness, a higher percentage of stage 1 sleep, a smaller percentage of REM sleep, and less REM activity when compared to patients with nonpsychotic major depression. A more recent study (63) found a greater percentage of intermittent wakefulness in patients with psychotic major depression than in patients with nonpsychotic major depression. When EEG spectral analysis was used, more specific, significant differences between patients with psychotic and nonpsychotic major depression emerged. The patients with psychotic major depression had greater power in the higher band widths, or "micro arousals," which could not be attributed to actual differences in awake time, since manually scored records did not show that awake time was significantly different between the two patient groups. The greater power observed in the higher band widths among the patients with psychotic major depression suggested that the arousal level may be a potentially distinguishing feature of these patients. The patients with psychotic major depression also appeared more likely to have extremely short sleep-onset REM latencies than the patients with nonpsychotic major depression. One study (64) did not find any statistically significant differences in sleep profiles between patients with psychotic and nonpsychotic major depression.

The diminished generation of REM sleep seen in patients with psychotic major depression may indicate a functional hyperactivity of central dopaminergic systems, since administration of dopaminergic agonists to normal control subjects results in increased arousal and considerable suppression of REM sleep (65). It is also of interest that a 1-mg dose of dexamethasone results in a 20% reduction of REM sleep in patients with nonpsychotic major depression (66), a reduction of about the same magnitude as the difference observed between patients with psychotic and nonpsychotic major depression (62). Thus, the decreased generation of REM sleep in patients with psychotic major depression may be secondary to corticosteroid/dopamine interactions (see preceding section). In any case, sleep EEG studies provide further evidence for considering psychotic major depression as a distinct subtype of major depression.

### *Measures of Serotonergic Function*

Differences between patients with psychotic and nonpsychotic major depression on measures of serotonergic function have also been reported. Healy et al. (67) reported on measures of platelet serotonin uptake in a group of 28 patients with endogenous depression. Delusional and nondelusional patients differed in absolute values for rate of serotonin uptake into platelets. In addition, the delusional patients did not show the lowering of serotonin uptake rate that was observed in the endogenously depressed group as a whole. The difference between the patients with psychotic and nonpsychotic major depression was maintained after treatment was started but was not present after clinical recovery, suggesting a state rather than trait phenomenon.

Patients with psychotic major depression demonstrate higher CSF 5-HIAA levels than do patients with nonpsychotic major depression. In the study by Aberg-Wistedt et al. (42), a strong positive correlation between CSF levels of 5-HIAA and HVA was observed. These authors noted that the higher HVA/5-HIAA ratio in their patients with psychotic major depression suggested a primary problem in dopaminergic neurotransmission and a secondary effect on serotonergic neurons. The higher HVA/5-HIAA ratio in the patients with psychotic major depression is consistent with results of another study (68), which found that hallucinations in depressed patients were strongly associated with higher HVA/5-HIAA ratios. In contrast, one study (41) did not find that patients with psychotic and nonpsychotic major depression differed on measures of CSF 5-HIAA, and another study (47) did not observe differences between patients with psychotic and nonpsychotic major depression in urinary 5-HIAA levels. It is difficult at this point to determine whether differences in serotonin transmission between patients with psychotic and nonpsychotic major depression are independent of a disturbance in dopaminergic neurotransmission.

### *Summary*

In summary, a growing body of evidence from studies of the HPA axis, studies of dopaminergic activity, enzyme studies, CT and magnetic resonance imaging scans, EEG sleep profiles, and measures of serotonergic function points to distinct biological abnormalities in psychotic as compared to nonpsychotic major depression. Although many of the studies did not explore the possible effects of endogenous states on specific differences, several did, and these results suggest that biological differences between psychotic and nonpsychotic major depression are not due to differences in relative endogenicity (26, 29, 31, 44).

## FINDINGS IN FAMILY STUDIES

First-degree relatives of patients with psychotic major depression demonstrate higher rates of depression (7, 69) and the psychotic subtype (69) than do members of the families of patients with nonpsychotic major depression, although not all studies are in agreement (70). In addition, the relatives of patients with psychotic major depression are significantly (six times) more likely to have bipolar disorder than are the relatives of patients with nonpsychotic major depression (71). In some ways, the limited family data are less compelling than are the data from other categories of studies, and further studies are needed to confirm and extend these findings. The higher prevalence of bipolar disorder in the families of patients with psychotic major depression is intriguing in light of the association of bipolar illness with early-onset psychotic major depression (72, 73).

## COURSE AND OUTCOME

### *One-Year Follow-Up*

The course, prognosis, and outcome of patients with psychotic and nonpsychotic major depression differ. Several studies have noted poorer short-term outcome in psychotic than in nonpsychotic major depression. Robinson and Spiker (74), in a prospective study, found that significantly more patients with psychotic major depression showed a pattern of chronic illness during the first posthospitalization year. They compared 52 patients with unipolar psychotic major depression and 52 patients with unipolar nonpsychotic major depression who were matched for sex, age at index episode of depression, and age at first episode of depression. In a 1-year follow-up after discharge from inpatient treatment, the patients with psychotic depression had a significantly higher rate of episodes of major depression lasting longer than 9 months than did the patients with nonpsychotic depression. The patients with psychotic major depression also were more likely to be in a major depressive episode at 1-year follow-up. Consistent with the poorer clinical response of the patients with psychotic major depression, there was a trend for them to have a higher total number of hospitalizations over the 1-year follow-up period. Murphy (75) also reported a poorer 1-year outcome for geriatric patients with psychotic major depression than for those with nonpsychotic major depression. Kettering et al. (76) found that the course of psychotic and affective symptoms in psychotic major depression differs from that in nonpsychotic major depression. In their study of patients with psychotic and nonpsychotic major depression, affective and anxiety symptoms made a smaller contribution to the total clinical picture in the patients with psychotic major depression 1 year after discharge. However, these patients were more likely to demonstrate mood-incongruent delusions at 1 year.

Recently, our group (77) reported that at 1-year follow-up, patients with the diagnosis of psychotic major depression at baseline did not differ from patients with nonpsychotic major depression on measures of depressive, anxious, or psychotic symptoms. However, the patients who had originally met the criteria for psychotic major depression demonstrated significantly poorer functioning at 1 year, as measured by the total score on the Social Adjustment Scale. There were significant correlations between higher urinary free cortisol levels at 1 year and poorer overall functioning at 1 year.

Recent data from the Epidemiological Catchment Area study (18) provide further evidence for a different course of illness in psychotic and nonpsychotic major depression. Patients with psychotic major depression had a greater risk of multiple episodes of depression than patients with nonpsychotic major depression (73.7% versus 61.9%, $p<0.05$). In addition, the patients with psychotic major depression had significantly greater economic impairment: more of them were receiving public assistance (17.5% versus 7.2%, $p<0.01$) and/or disability payments (15.9% versus 6.7%, $p<0.01$). Psychotic major depression was not associated with significantly more reports of economic impairment due to emotional, alcohol, or drug problems than was nonpsychotic major depression (5.7% versus 3.6%, n.s.). The patients with psychotic major depression had a higher lifetime rate of psychiatric hospitalization (22.8% versus 14.7%, $p<0.05$) and a greater risk of hospitalization for medical reasons in the last year. At 1-year follow-up, the patients with psychotic major depression were more likely to be currently depressed (in the last month, 18.7% versus 11.1%, $p<0.05$) and to be still financially dependent (27.4% versus 11.2%, $p<0.01$).

### *Longer-Term Follow-Up (2 Years or More)*

In the Iowa 500 study, Coryell and Tsuang (78) found that the initial presence of delusions predicted a poorer short-term (2–5-year) outcome, whereas a 40-year follow-up with structured interviews found no consistent trends distinguishing psychotic from nonpsychotic patients with major depression on ratings of marital, occupational, residential, or symptom outcome. In the National Institute of Mental Health (NIMH) Clinical Research Branch Collaborative Program on the Psychobiology of Depression study, Coryell et al. (79) reported that despite substantially greater levels of impairment during the 5 years preceding intake into the study, patients with unipolar psychotic major depression were as likely to recover as were patients with unipolar nonpsychotic major depression during a 2-year follow-up period. The patients with psychotic major depression were more psychosocially impaired at 6 months, but these differences resolved during the ensuing 18 months. In a 5-year follow-up of the patients reported previously by Coryell et al. (79, 80), significantly greater social impairment, but not depression, was observed in the patients with psychotic major depression (81).

### *Bipolar Disorder*

Psychotic major depression with onset in adolescence or young adulthood appears to be related to bipolar disorder. Akiskal et al. (73) reported on the follow-up of a group of depressed patients who had not had histories of mania at the time of the index study (i.e., they had unipolar illness). The prevalence of baseline psychotic depression was significantly greater ($p<0.01$) among the patients who developed bipolar illness during follow-up (42%) than among those who did not (15%). Similarly, Strober and Carlson (72) reported that the appearance of bipolar disorder in adolescents originally studied when depressed was predicted by a depressive symptom cluster comprising mood-congruent psychotic features, rapid symptom onset, and psychomotor retardation. These data suggest that psychotic major depression in a young adult may often prove to be the first episode of a bipolar disorder.

### *Recurrent Psychotic Episodes*

Studies have demonstrated a remarkable consistency over time in the clinical presentation of patients with psychotic major depression. Charney and Nelson (12), reporting on 54 patients with unipolar psychotic major depression and 66 patients with unipolar nonpsychotic major depression, found that for the patients with psychotic depression, 89% of all prior depressive episodes were psychotic, compared to only 12% for the group with nonpsychotic depression ($p<0.001$). In addition, examination of the prior depressive episodes of the patients with psychotic major depression indicated that the delusions of these patients tended to be of similar form and content from episode to episode. An earlier study (11) of 14 patients with unipolar psychotic major depression also found that the episodes of depressive illness in each patient were characterized by similar symptoms (including the specific content of the delusions).

## TREATMENT

The patterns of response to somatic therapies among patients with psychotic major depression are quite different from those among patients with nonpsychotic major depression (for reviews of this subject, see 3–5, 9, 11, 82, 83). Although most reports on somatic therapy of psychotic major depression have been the result of open trials or retrospective reviews, the past few years have witnessed a few double-blind studies. Overall, the literature points to a number of reasonable conclusions regarding the somatic treatment of psychotic major depression.

1. Patients with psychotic major depression respond

poorly to placebo. Placebo response rates appear higher among patients with nonpsychotic major depression.

2. In contrast to patients with nonpsychotic major depression, patients with psychotic major depression respond poorly (or at best very slowly) to tricyclic antidepressants when these are administered alone.
3. Patients with psychotic major depression who fail to respond to tricyclic antidepressants respond to ECT. However, ECT may not be more effective in these patients than in patients with nonpsychotic major depression.
4. Patients with psychotic major depression respond better to the combination of a tricyclic antidepressant with a neuroleptic than they do to a tricyclic antidepressant alone.
5. Patients with psychotic major depression respond as well to amoxapine (a four-ring tricyclic-like antidepressant with serotonin-2 receptor-blocking properties and a neuroleptic metabolite) as to the combination of a tricyclic antidepressant and a neuroleptic.

### *Placebo*

Glassman and Roose (9) reported that patients with psychotic major depression did not demonstrate responses to placebo. The placebo washout period was the initial phase of protocols designed to explore the relation of plasma levels of imipramine to response to antidepressants. Eighteen (30%) of 60 patients with nonpsychotic major depression responded to placebo, in contrast to none of 21 patients with psychotic major depression. In a recent study, Anton and Burch (83) reported that 10% of patients with psychotic major depression responded during placebo washout. Unfortunately, these studies were single-blind during the placebo phase, making definitive conclusions difficult. In another study, Chan et al. (82) reported that 19 of 59 nonpsychotic depressed patients responded during a 2-week washout period, in contrast to three of 16 patients with psychotic major depression. These three patients with psychotic major depression demonstrated only partial responses.

### *Tricyclic Antidepressants Alone*

Early studies on tricyclic antidepressant therapy in depression noted that depressed patients with psychotic features responded poorly to imipramine or amitriptyline (84–86). Those observations were largely overlooked until the studies by Glassman et al. of plasma levels of imipramine. These investigators administered fixed milligram-per-kilogram doses of imipramine to both psychotic and nonpsychotic patients with major depression and also observed that patients with psychotic major depression responded more poorly to imipramine (87). Specifically, three (23%) of 13 patients with psychotic major depression responded, in contrast to 14 (67%) of 21 patients with nonpsychotic major depression. This difference was statistically significant and was not due to severity of illness.

In a landmark study, DeCarolis (88) administered imipramine to 437 depressed patients. The patients were treated with 200–350 mg/day of the drug for at least 25 days, and those who did not respond after 30 days were treated with ECT. Patients with psychotic major depression did more poorly on the regimen of imipramine (40% response rate) than did endogenous and neurotic-reactive depressed patients (61% and 60%, respectively). Subsequently, a number of studies (many of them retrospective reviews) again confirmed that patients with psychotic major depression respond more poorly to tricyclic antidepressants alone than do patients with nonpsychotic major depression (8, 12, 82). Indeed, in their report, Chan et al. (82) reviewed response data on more than 1,000 depressed patients from 12 studies, including their own (7, 12, 82, 85, 86, 88–94). They calculated that 127 (35%) of 363 patients with psychotic major depression responded to tricyclic antidepressant therapy, in contrast to 464 (67%) of 691 patients with nonpsychotic major depression ($\chi^2$=104.2, df=1, $p<2\times10^{-24}$). These results do not appear to be due to a general pattern of underdosing.

We have identified an additional two studies that were not included in the review by Chan et al. One (8) appeared before the Chan et al. study; the other (95), after. Both studies found lower response rates to tricyclic antidepressants among patients with psychotic major depression than among patients with nonpsychotic major depression. Frances et al. (8), in a retrospective chart review, reported that three of 18 patients with psychotic major depression responded to tricyclic antidepressants, in contrast to 17 of 23 patients with nonpsychotic major depression ($\chi^2$=10.8, df=1, $p<0.001$). In the NIMH Collaborative Program on the Psychobiology of Depression study (95), imipramine or amitriptyline was administered for 4 weeks to 132 patients. We recalculated the response rates of the patients with psychotic and nonpsychotic major depression in this study and found that they were lower (albeit of trend significance, p=0.06) among those with psychotic major depression (32% versus 55%). In addition to all these reports of studies that have compared patients with psychotic and nonpsychotic major depression, there have been several other reports that patients with psychotic major depression respond poorly to tricyclic antidepressants (96–98).

There are two notable exceptions to the finding that patients with psychotic major depression respond more poorly to tricyclic antidepressants than do patients with nonpsychotic major depression. Quitkin et al. (99) reanalyzed a previous study by Klein (100) that had compared 6 weeks of treatment with imipramine versus placebo for depressed patients. They concluded that delusions did not predict poor response to imipramine and argued that patients with psychotic major depression often required treatment for prolonged periods and at higher dosages. (Most studies have used 4 weeks of treatment with tricyclic antidepressants.) This reanalysis has been criticized for its retrospective definition of psychotic and nonpsychotic groups, which used the F factor of the Lorr Multidimensional Scale for psychiatric patients. The F factor includes items that do not concern delusions (e.g., poor orientation and hostile impulses), raising questions about the accuracy of the retrospectively performed diagnoses (8, 9, 82). However, Klein, in a personal communication to us, has indicated that these patients were psychotic.

In a retrospective review of patients treated for up to 9 weeks, Howarth and Grace (94) reported that patients with psychotic major depression responded significantly better to tricyclic/tetracyclic antidepressants than did patients with nonpsychotic major depression. Twenty-one (62%) of 34 psychotic patients responded, in contrast to nine (41%) of 22 nonpsychotic patients. The patients with psychotic major depression, however, responded more slowly to treatment; the authors estimated that more than 40% may require treatment for at least 4–9 weeks. Many of the other previous studies had used shorter treatment periods, e.g., 4 weeks. These data indicate that the nature of the response to tricyclics differs in the two groups but that some delusional patients may do well when given tricyclic antidepressants if they are prescribed for sufficient periods.

Several studies have explored whether the poorer responses observed with tricyclic antidepressant therapy were due to the effects of severity or endogenicity. Glassman et al. (90) noted slightly lower response rates (56%) for patients with more severe nonpsychotic major depression (total Hamilton Rating Scale for Depression score greater than 27) than for patients with less severe nonpsychotic major depression (75%); however, this difference was not statistically significant. Chan et al. (82) reported that degree of incapacitation or endogenous status failed to predict poor response to tricyclic antidepressants, in contrast to delusional status, which did.

On the other hand, in the NIMH Collaborative Program on the Psychobiology of Depression study (95), the response rate to tricyclic antidepressant therapy differed significantly among patients with psychotic major depression, nonpsychotic moderately depressed patients (defined as having a total Hamilton depression score of 26 or less), and nonpsychotic severely depressed patients (Hamilton depression score greater than 27). The nonpsychotic severely depressed patients did not differ significantly from the patients with psychotic major depression in their response rates (32% and 39%, respectively). The total Hamilton depression scores of the nonpsychotic severely depressed patients were similar to those of the patients with psychotic major depression, suggesting that general severity of illness could be a factor in why patients with psychotic major depression respond poorly to tricyclic antidepressants. The nonpsychotic moderately depressed patients did significantly better than the combined group of patients with psychotic major depression and nonpsychotic severely depressed patients. There are a number of caveats regarding this study. In contrast to most of the other studies, it combined patients with unipolar and bipolar illness. In addition, the severely ill nonpsychotic group was significantly older than the moderately ill nonpsychotic group and the patients with psychotic depression.

The DeCarolis study (88) also suggested that severity may predict poor response. As we have indicated, patients with psychotic major depression responded more poorly on a regimen of imipramine (40% response rate) than did endogenous and neurotic-reactive depressed patients (61% and 60%, respectively). However, patients designated as being severely depressed also did poorly (35% response rate). Since in this study patients may not have been placed into discrete categories for analyses (i.e., the same patients were probably classified as both delusional and severely ill), it is difficult to comment on the relative effects of severity on response to treatment. The data from this study suggest, however, that the poorer responses to imipramine among patients with psychotic major depression are not merely due to endogenous symptoms. The role of severity in determining poor responsiveness of patients with psychotic major depression to tricyclic antidepressants requires further study.

### *ECT*

A number of lines of investigation suggest that ECT is an effective treatment for psychotic major depression. Many retrospective clinical reports point out that patients with psychotic major depression who respond poorly to tricyclic antidepressants do well when subsequently treated with ECT (6, 8, 12, 87, 92, 93, 96, 97, 101). For example, Glassman et al. (87) reported that nine of the 10 patients with psychotic major depression who had failed to respond in their prospective imipramine study responded well to ECT. This finding was perhaps most dramatic in the DeCarolis study (88). As we have mentioned, in that study only 40% of the patients with psychotic major depression responded to initial treatment with imipramine. However, 83% of the nonresponders then responded to ECT. A high rate of response to ECT was also observed among severely depressed patients who had responded poorly to imipramine, although, again, there may have been great overlap between the psychotic and severely depressed groups of patients. In contrast, patients with neurotic-reactive depressions responded well to imipramine, and patients who failed to respond to imipramine generally did not respond to ECT.

Avery and Winokur (91) reviewed hospital records of 59 depressed patients hospitalized between 1959 and 1969. Forty-two percent of the depressed patients with delusions responded to ECT; in contrast, only 18% responded to adequate antidepressant trials ($p<0.05$). The delusional group included some patients with nondepressive hallucinations or delusions (i.e., schizoaffective patients), making comparison of this study to others somewhat difficult.

Four studies have compared response to ECT among patients with psychotic versus nonpsychotic major depression. Rich et al. (102, 103) and Brown et al. (93) found ECT to be equally effective for patients with psychotic and nonpsychotic major depression. However, Charney and Nelson (12) reported that response to

ECT was better in patients with psychotic major depression than in their counterparts with nonpsychotic major depression. Taken together, these data suggest that ECT is an effective treatment for psychotic depression. However, it may not be more effective for patients with psychotic major depression than for nonpsychotic severely depressed patients.

### *Tricyclic Antidepressant/Neuroleptic Combination*

In both retrospective and prospective studies, the combination of a tricyclic antidepressant and a neuroleptic has been reported to be an effective treatment for psychotic major depression. Several groups have reported that patients who had failed to respond to tricyclic antidepressants alone went on to respond to the combination of a tricyclic antidepressant and a neuroleptic (8, 12, 96).

Spiker et al. (5) compared the combination of amitriptyline and perphenazine, amitriptyline alone, and perphenazine alone in the treatment of patients with psychotic major depression. Mean daily doses were 218 mg of amitriptyline alone, 50 mg of perphenazine alone, and for the combination, 170 mg of amitriptyline and 54 mg of perphenazine. The protocol called for 35 days of active treatment. Fourteen (78%) of 18 patients treated with the combination responded, in contrast to seven (41%) of 17 patients treated with amitriptyline and three (19%) of 16 patients treated with perphenazine. Seven of the 13 patients who failed to respond to perphenazine were not psychotic at the completion of the study but were still depressed. A high proportion of the patients who had failed to respond to either amitriptyline or perphenazine alone responded when the other drug was added. Differences between responses to the combination and to each ingredient alone were not due to one compound raising the blood level of the other. This study included patients with both bipolar and unipolar psychotic depression.

### *Amoxapine*

Recently, Anton and Burch (83) reported that in psychotic depression, amoxapine, a four-ring compound that is related to the antipsychotic loxapine, was comparable in efficacy to the combination of amitriptyline and perphenazine. This study was undertaken after open trials suggested 60%–80% response rates to amoxapine in patients with psychotic major depression (104). After a single-blind, 5-day placebo washout period, patients were randomly assigned to receive amoxapine or the combination of amitriptyline and perphenazine under double-blind conditions. The maximum daily dose of amoxapine was 400 mg; for the combination, the maximum was 200 mg of amitriptyline and 32 mg of perphenazine. Eighty-two percent of the amoxapine group and 85% of the amitriptyline/perphenazine group demonstrated moderate to marked improvement. The combination produced significantly more extrapyramidal side effects, and there was a tendency for it to produce more anticholinergic side effects. The authors noted that the ratio of serotonin-2 to dopamine-2 receptor blockade of amoxapine was similar to that of a number of atypical neuroleptics, suggesting a possible mechanism of action for the antipsychotic effect of this compound.

### *Summary*

In summary, studies on psychotic depression indicate that the condition responds 1) infrequently to placebo, 2) poorly (or, at best, very slowly) to tricyclic antidepressants alone, and 3) well to ECT, to the combination of a tricyclic antidepressant and a neuroleptic, and to amoxapine alone. In contrast, patients with nonpsychotic major depression demonstrate higher response rates to both placebo and tricyclic antidepressants alone than do patients with psychotic major depression. The relative contribution of severity of illness as a factor in lowering responsiveness to tricyclic antidepressant therapy still requires further study.

## DISCUSSION AND CONCLUSIONS

The major efforts expended in recent decades toward developing clinically valid classification systems resulted in the inclusion of a large number of syndromes in *DSM-III-R*, for many of which there are relatively limited data on the key dimensions (e.g., biology and response to treatment) that are necessary for validating their designation as distinct disorders. Indeed, some investigators have argued that many *DSM-III-R* disorders would be better classified under a broader rubric of affective disorder (105). In contrast, the data reviewed in this article strongly suggest that unipolar major depression with psychotic features is a disorder that can be differentiated from unipolar major depression without psychotic features on a number of important dimensions—particularly symptoms, biological characteristics, course/outcome, and response to treatment.

Still, a number of questions can and should be raised about a separate designation. For one, could the so-called differentiating characteristics of psychotic versus nonpsychotic major depression merely be separating a more severe from a less severe disorder rather than demarcating a truly distinct syndrome? As we have indicated in detail, severity alone did not appear to account for the differences between psychotic and nonpsychotic major depression. For example, in regard to symptom characteristics, Coryell et al. (1) reported significantly higher total scores on the 17-item Hamilton Rating Scale for Depression among patients with psychotic major depression than among patients with nonpsychotic major depression, but these differences were mainly due to three items concerning delusions. In that study, psychomotor disturbance was the only somatic symptom to separate the two groups. Patients with psychotic major depression did not demonstrate significantly higher scores on the remaining neurovegetative symptoms. The differences in HPA activity (34), sleep (62), and response to treatment (82, 90) between patients with psychotic and nonpsychotic major depression also did not appear to be due to differences in severity. However, particularly in regard to treatment, further prospective investigation is required, since some studies have also reported poor responses to tricyclic antidepressants in severely ill patients with nonpsychotic major depression (88, 95).

Could the differences between psychotic and nonpsychotic major depression be due to differences in endogenicity? This is an important issue, since guilt feelings and psychomotor disturbance are clearly endogenous symptoms. A few studies explored the specific role of endogenicity, and these also failed to demonstrate that differences between psychotic and nonpsychotic major depression were due to more intense endogenous-type symptoms in the former. Indeed, the recent article by Parker et al. (16), on a well-defined group of patients who met the RDC for endogenous depression and the *DSM-III* criteria for melancholic depression, clearly indicated that the differentiating symptoms do not merely separate endogenous from nonendogenous (or more endogenous from less endogenous) disorders. Moreover, data from a number of studies on HPA activity (26, 29, 34) and response to treatment (82, 88) also failed to substantiate that differences were due to endogenicity and not to psychosis.

The findings that young patients with psychotic major depression are at high risk for developing bipolar disorder (72, 73) and that there is increased risk of bipolar disorder in the families of patients with psychotic major depression (71) could suggest that psychotic major depression should be classified as a bipolar disorder. There are a number of arguments against this designation, however. For one, the relatively high risk of a switch into mania has been described in adolescent but not older patients. Thus, only in younger patients does psychotic major depression potentially signify the first episode of a bipolar disorder. Although the prevalence of psychotic major depression is higher among bipolar than unipolar patients (1), this observation does not negate the observations that unipolar psychotic and nonpsychotic major depressive disorders can be differentiated. One could argue that the differences between psychotic and nonpsychotic major depression merely reflect the differentiation of a forme fruste bipolar psychotic depression from unipolar nonpsychotic major depression. However, data from our group and others point to differences between patients with unipolar and bipolar psychotic major depression in cortisol (27) and dopamine β-hydroxylase (49, 106) activity. Although further studies are required, the limited data gathered so far suggest that unipolar psychotic major depression differs from bipolar psychotic major depression.

An argument can be made that there is little to be gained from having another *DSM-IV* category rather than continuing a dimensional designation for psychosis. Although many technical issues regarding a categorical versus a dimensional designation of psychotic major depression (107) have not been explored, data on morbidity and response to treatment point to the practical need for clearer separation of this disorder. Furthermore, the difficulty in making the diagnosis results in its being frequently missed in the clinical setting, with patients receiving less than optimal treatment and having poorer outcomes (108). A separate designation with clear criteria would assist patients and practitioners alike.

Although we believe that a separate designation would be beneficial, further research on the potentially demarcating symptoms as well as other key dimensions (e.g., biology and response to treatment) is necessary to develop an optimal set of criteria and to resolve lingering questions about severity, endogenicity, bipolarity, and optimal treatment. Nevertheless, the data reviewed in this article point to both the rationale and the need for designating psychotic major depression as a distinct syndrome in *DSM-IV*.

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# G Proteins: Implications for Psychiatry

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*There is mounting evidence that a family of guanosine triphosphate binding proteins (G proteins) play an obligatory role in the transduction of a vast array of extracellular, receptor-detected signals across cell membranes to intracellular effectors. The author reviews the literature dealing with G protein coupling to second messenger generation, the role of G proteins in regulating both the convergence and divergence of neurotransmitter action in the CNS, and the involvement of G proteins in a variety of clinical conditions, with an emphasis on psychiatric conditions and their treatments. G proteins form the basis of signal integration in the CNS, endowing the neuron with a large degree of functional diversity. Abnormalities in the function and/or expression of G proteins have been implicated in a variety of pathophysiologic states, and a number of currently available psychotropic drugs affect G proteins. The understanding of the mechanisms by which G proteins modulate neuronal activity may be one of the keys to understanding the functioning and the complexities of the nervous system. Given their widespread, critical roles in the regulation of neuronal function, it seems likely that G proteins are involved in the pathophysiology of various major psychiatric illnesses. The development of novel, site-specific drugs with primary G protein targets remains an exciting prospect for the future.*

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One of the most exciting recent advances in neuroscience has been the elucidation of the molecular mechanisms underlying neuronal communication. Although rapidly increasing numbers of potential neurotransmitters and receptors continue to be identified, it has become clear that the translation of the extracellular signals (into a form that can be interpreted by the complex intracellular enzymatic machinery) is generally achieved in relatively few ways. Generally speaking, these transmembrane signaling systems, and the receptors that use them, can be divided into two major groups:

1. Those with relatively self-contained structures and messages that take the form of transmembrane ion fluxes.
2. Those with multiple components and messages that generate various intracellular "second messengers."

The first class of receptors contain in their stable molecular complex an intrinsic ion channel. Receptors of this class include those for a number of amino acids—including glutamate, γ-aminobutyric acid (GABA) (through the $GABA_A$ receptor), and glycine—the nicotinic acetylcholine receptor, and the $5\text{-}HT_3$ receptor (1). Receptors of this type have also been described as "ionotropic" and are generally composed of four or five subunits surrounding a central ionic pore, which opens transiently when the transmitter binds, allowing ions to flow either into the neuron (e.g., $Na^+$, $Ca^{+2}$, $Cl^-$) or out of it (e.g., $K^+$), thereby generating synaptic potentials. Neurotransmission of this type is very fast: ion channels open and close within milliseconds (2).

Most receptors, however, do not have ionic conductance channels within their structure; rather, they regulate cellular activity by generating various second messengers. In general, receptors of this class do not directly interact with the various second-messenger-generating enzymes but transmit information to the appropriate "effector" by the activation of interposed "coupling proteins." It is now clear that a family of structurally related, guanosine-triphosphate-binding proteins (or G proteins) play an obligatory role in the transduction of a vast array of extracellular, receptor-detected signals across cell membranes to intracellular effectors. Indeed, Birnbaumer (3) has suggested that about 80% of all known hormones, neurotransmitters, and neuromodulators (numbering around 100) elicit cellular responses through G proteins coupled to a variety of cellular effectors, including adenylyl cyclase (frequently referred to as adenylate cyclase), phospholipase C, phospholipase $A_2$, and several ion channels (4). Receptors coupled to G proteins include those for catecholamines, serotonin, acetylcholine, various peptides (e.g., vasopressin, substance P), and even sensory signals, such as light and various odorants (3). Receptors coupled to G proteins are prototypic "metabotropic" receptors. Activation of these receptors initiates a cas-

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cade of events, usually through regulation of intracellular second messengers, that lead to modification of enzymatic phosphorylation of various membrane and cytosolic proteins (enzymatic activation or inhibition), including receptors, ion channels, and possibly G proteins themselves (1). As might be predicted, receptors coupled to G proteins generate electrical signals much more slowly, often with a latency of signal onset of at least 30 msec (2). The ability of many G proteins to interact with multiple receptors also provides an elegant mechanism for the neuron to respond to a large number of stimuli and to regulate both the convergence and divergence of neurotransmitter action (5, 6). The high degree of complexity generated by the interactions of G-protein-coupled receptors may be one mechanism by which neurons acquire the flexibility necessary for generating the wide range of responses observed in the nervous system; this has led to the suggestion that G-protein-coupled receptors may be involved in pathways regulating such diverse vegetative functions as mood, appetite, and wakefulness (2).

Thus, understanding the mechanisms by which G proteins modulate neuronal activity is one of the keys to understanding the functioning and the complexities of the nervous system. Additionally, there is a growing body of evidence implicating both quantitative and qualitative G protein abnormalities in a variety of clinical disorders. Similarly, there is increasing evidence that a number of psychotropic agents exert their clinically relevant effects at postreceptor sites, including G proteins. The identification of these putative G protein targets may thus lead not only to the development of more potent, site-specific treatments but also to the localization of molecular and biochemical factors predisposing individuals to various psychiatric illnesses.

This overview will explore the growing knowledge of G protein coupling to chemical and ionic second messenger generation. Specifically, I will discuss the biochemistry of second messenger synthesis, the role of G proteins in neurotransmitter-neurotransmitter interactions, and the possible involvement of G proteins in a variety of clinical conditions, with an emphasis on psychiatric conditions and their treatments.

## WHAT ARE G PROTEINS?

The G proteins are a family of GTP-binding proteins that play an obligatory role in the transduction of extracellular, receptor-detected signals across the cell membrane to various intracellular effectors (3, 4). These proteins have been the focus of extensive research since the demonstration that stimulation of adenylyl cyclase (the enzyme which generates cAMP) activity requires both hormones and GTP. It was subsequently demonstrated that β-adrenergic agonists stimulated GTPase activity (discussed later) in erythrocytes and that guanine nucleotides—such as GTP or similar nonhydrolyzable analogues [Gpp(NH)p or GTPγS]—modulated the affinity of this receptor for agonists but not antagonists. These and other indirect observations led to the proposal that the site of GTP's action is on a protein distinct from both the hormone receptor and adenylyl cyclase.

This hypothesis was confirmed by the subsequent purification of a GTP-binding protein from liver. By using the S49 cell mutant (deficient in hormone- and GTP-dependent activity), now termed "cyc$^-$," it was possible to demonstrate that the addition of the purified "transducer protein" restores hormone- and GTP-dependent adenylyl cyclase activity. Since the addition of this purified protein stimulated adenylyl cyclase activity, it was termed "$G_s$" (s=stimulatory) (reference 7 is an excellent historical overview). Shortly thereafter, the purification of a protein necessary for inhibition of adenylyl cyclase ("$G_i$") provided a mechanistic explanation for the bidirectional regulation of this enzymatic activity (8). $G_i$-like proteins were shown to activate a phospholipase C that hydrolyzes phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol and inositol 1,4,5-trisphosphate and to modulate the activity of specific ion channels (3, 4, 9, 10). Subsequently, another G protein for which no obvious function was evident was purified from brain (11); this protein was named "$G_o$" (o=other protein). The identification of $G_o$ led to the realization that the G proteins are, in fact, a family of homologous proteins serving diverse roles in a wide variety of receptor-mediated extracellular signals to various intracellular second messenger systems (3, 4, 9, 10). It is now clear that G proteins involved in signal transduction are αβγ heterotrimers. The greatest diversity observed thus far is with α subunits, which are generally believed to directly modulate the activities of various effectors (discussed later), but diversity also exists for β and γ subunits (see table 1).

## MECHANISM OF G PROTEIN ACTIVATION

The molecular events underlying G protein activation/deactivation have been best characterized for G-protein-mediated regulation of adenylyl cyclase (3, 4, 13), but the following sequence of events is assumed to occur for most (if not all) G proteins (see figure 1).

The G protein α subunit cycles between an inactive GDP-bound oligomeric (αβγ) form and an active GTP-bound monomeric form. Gilman (4, 13) has described these two forms of the α subunit as the "off" and "on" positions of a carefully timed molecular switch. Activation of a receptor by an agonist induces a conformational change in the receptor, allowing it to interact with the G protein, and forms a short-lived "high-affinity ternary complex" consisting of these components. The interaction of the receptor with the G protein in turn results in a conformational change in the α subunit of the G protein, which facilitates the displacement of GDP by GTP. The binding of GTP is a crucial step in the activation cycle and has two major consequences.

1. The G protein dissociates from the receptor. This destabilization of the high-affinity ternary complex re-

**TABLE 1. Key Features of G Protein Subunits[a]**

| Subunit | Molecular Weight ($\times 10^{-3}$) | Toxin Targeting Subunit (cholera or pertussis) | Effector(s)[b] | Examples of Receptors |
|---|---|---|---|---|
| $G\alpha_s$ (four types) | 44.5–46 | Cholera | AC (+); L-type $Ca^{+2}$ channels (+) | $\beta_1$, $\beta_2$, $D_1$, $A_2$, $H_2$, ACTH, CRH, $V_2$, $PGE_1$ |
| $G_{s,olf}$ | 44.7 | Cholera | AC (+) | Olfactory signals |
| $G\alpha_i$ (three types) | 40.4–40.5 | Pertussis | AC (–); $K^+$ channels (+) | $\alpha_2$, $D_2$, $A_1$, $\mu$, $M_2$, $5\text{-}HT_{1A}$ |
| $G\alpha_{t,r}$ | 40.5 | Both | Cyclic GMP phosphodiesterase (+) | Retinal rods (rhodopsins) |
| $G\alpha_{t,c}$ | 40.5 | Both | Cyclic GMP phosphodiesterase (+) | Retinal cones (rhodopsins) |
| $G\alpha_o$ (two types) | 39.9 | Pertussis | $K^+$ channels (+); $Ca^{+2}$ channels (–); PLC (+) (sensitive to pertussis toxin) | $\alpha_2$, $\mu$, $GABA_B$ |
| $G\alpha_z$ | 40.9 | Neither | PLC (+)[c] (insensitive to pertussis toxin) | Unknown |
| $G_q$, $G_{11}$, $G_{14}$ | 42 | Neither | PLC (+) (insensitive to pertussis toxin) | Thromboxane $A_2$, vasopressin |
| $\beta$ (four types) | 37.4 | Neither | Direct interaction with AC (–)[c]; inactivates $\alpha_s$ | |
| $\gamma$ (three types) | 8–10 | Neither | $\beta\gamma$ required for interaction of $\alpha$ subunit with receptor | |

[a] Adapted from Birnbaumer (3), Taylor et al. (9), Freissmuth et al. (10), and Strathmann and Simon (12).

[b] AC=adenylyl cyclase, PLC=phospholipase C, +=stimulatory effect of subunit on effector, –=inhibitory effect.

[c] Finding uncertain.

sults in the receptor's reversion to the low-affinity conformation and the dissociation of the agonist from the receptor. Thus, the receptor is not permanently associated with the $G_s$-adenylyl cyclase complex, and this allows the receptor to recycle and function catalytically, activating several G proteins during the time that one $G_s$ remains active.

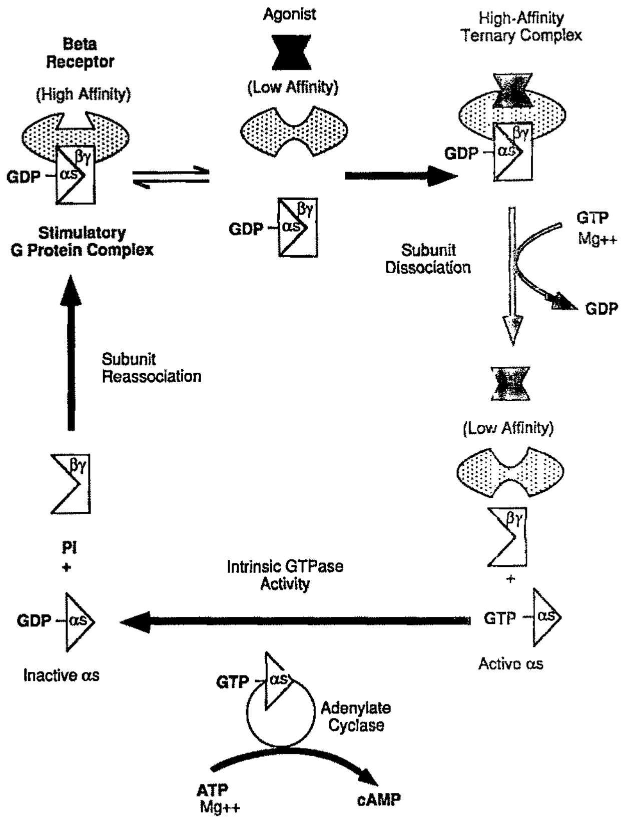
2. The second major consequence of GTP binding to the G protein is to promote dissociation into $\alpha$-GTP and $\beta\gamma$ subunits. It is generally accepted that, for a number of effector systems, the $\alpha$-GTP complex activates the effector enzyme by an as yet undetermined mechanism. The continued activation of adenylyl cyclase by $\alpha$-GTP is terminated by the action of a GTPase enzyme intrinsic to the $\alpha$ subunit, which hydrolyzes GTP to GDP. However, this process is relatively slow, allowing for additional amplification of the signal. The formation of $\alpha$-GDP is presumed to cause dissociation of $\alpha_s$ from the effector (which is now free to interact with additional activated $\alpha$-GTP subunits); the reassociation of $\alpha$-GDP with $\beta\gamma$ is thermodynamically stable and completes the cycle with the formation of the inactive GDP-bound holo-G protein.

Receptors appear to exert their inhibitory effects on adenylyl cyclase by two distinct mechanisms. First, in a manner closely paralleling that just outlined for $G_s$, there appears to be a direct inhibitory effect of $\alpha_i$ on the catalytic unit of adenylyl cyclase. Gilman (4, 13) has proposed that, in addition to the direct inhibition by $\alpha_i$, the $\beta\gamma$ subunits, released by receptor activation of $G_i$, may by mass action attenuate the dissociation of $G_s$. Since the quantity of $G_i$ is considerably greater than the quantity of $G_s$ in most tissues and $\beta\gamma$ subunits appear to be largely interchangeable, this sequestration model has received much acceptance. Although some debate persists as to whether the $\alpha_i$ or $\beta\gamma$ subunits have the greater role in the inhibition of adenylyl cyclase, more studies suggest that they exert distinct but complementary effects in the inhibition of adenylyl cyclase. Thus, $\beta\gamma$ subunits may be more potent inhibitors of receptor-independent stimulation of adenylyl cyclase (14). It is thus possible that $\alpha_i$ is the primary mediator of inhibition of adenylyl cyclase when $G_s$ is stimulated by a hormone or neurotransmitter but that $\beta\gamma$ exerts a major role in the inhibition of basal and postreceptor-stimulated adenylyl cyclase activity.

## G PROTEINS AS TARGETS FOR BACTERIAL TOXINS

The discovery that certain bacterial toxins (in particular, pertussis and cholera) can covalently modify selected G proteins has been invaluable in the delineation of various structural and functional aspects of highly homologous G proteins. In brief, both cholera toxin and pertussis toxin catalyze the transfer of an adenosine diphosphate ribose (ADP-ribose) moiety onto the $\alpha$ subunits of various G proteins. These ADP-ribosylation reactions, and their subsequent effects on signal transduction, are believed to be responsible (at least in part) for the pathophysiology of the diarrhea and whooping cough caused by cholera toxin and pertussis toxin, respectively. A major difference between the stimulatory ($G_s$) and other subtypes of G proteins is their susceptibility to toxin-catalyzed ribosylation. The $\alpha$ subunits of $G_s$ and $G_t$ (transducin, the major retinal G protein) are substrates for ADP-ribosylation by cholera toxin (3, 13). $G_i$ is not generally a target of cholera toxin; rather, it is preferentially ADP-ribosylated in an analogous manner by pertussis toxin. ADP-ribosylation by pertussis toxin appears to stabilize the G protein in its inactive $\alpha\beta\gamma$ undissociated conformation. Additionally, pertussis toxin "uncouples" receptors from $G_i$ (3, 4, 7), thereby attenuating receptor-mediated inhibition of adenylyl cyclase. Studies using cDNA cloning have shown that several G proteins are substrates for pertussis toxin, namely, $G_{i1}$, $G_{i2}$, $G_{i3}$, $G_t$, and $G_o$ (15). Thus, additional techniques have to be used to distinguish between the various pertussis toxin substrates. Nevertheless, the relative selectivity of these toxins has resulted in their extensive use in identifying the presence of $G_s$ and $G_i$ in various tissues, as well as the coupling of various receptors to these G proteins.

**FIGURE 1. Mechanisms of G Protein Activation/Deactivation**[a]



[a] At rest an equilibrium exists between the receptor in the high-affinity state (coupled to the G protein) and the low-affinity state. Activation of receptors by an agonist induces a conformational change in the receptor, allowing it to interact with the G protein, and forms a short-lived "high-affinity ternary complex" consisting of these components. The receptor-G protein interaction facilitates the replacement of GDP by GTP on the guanine nucleotide site (on the α subunit of the G protein). Binding of guanine nucleotides to the G protein causes a destabilization of the high-affinity complex and a dissociation of the G protein into α-GTP and βγ subunits. For most effector systems, the α-GTP complex activates the enzyme or ion channel. The continued activation is terminated by the action of a GTPase enzyme intrinsic to the α subunit, which hydrolyzes GTP to GDP; the reassociation of GDP-α with βγ completes the cycle with the formation of the inactive G protein.

## G PROTEIN REGULATION OF PHOSPHOLIPASE C

The phosphoinositide pathway is a major signal-transducing pathway that has a ubiquitous role in the regulation of various aspects of cellular and neuronal function. The binding of hormones and neurotransmitters to a variety of cell surface receptors—e.g., $\alpha_1$-adrenergic, serotonin ($5\text{-HT}_{1c}$, $5\text{-HT}_2$), and muscarinic ($M_1$, $M_3$)—activates, through interposed G proteins, a phosphoinositide-specific phospholipase C (16). This enzyme hydrolyzes phosphatidyl inositol 4,5-bisphosphate ($PIP_2$) to generate two second messengers: inositol 1,4,5-trisphosphate ($IP_3$), which mobilizes $Ca^{+2}$ from intracellular stores, and 1,2-diacylglycerol, which activates protein kinase C (16). Protein kinase C occupies a pivotal position in the biochemical pathways that relay information into the cell, because it is able to influence the cellular response to numerous other stimuli. Indeed, activation of protein kinase C has been linked to the regulation of cell surface receptors, ion channels, secretion, gene expression, and neuronal plasticity (17). The details of the phosphoinositide turnover pathway have been outlined previously in an excellent review in the *Journal* (17) and will not be repeated here.

The G protein that stimulates phosphoinositide turnover has been termed "$G_p$" (p=phosphoinositide), although its exact nature remains to be determined. What is clear, however, is that there appears to be more than one type of G protein activating phospholipase C, since pertussis toxin (which ADP-ribosylates and inactivates several G proteins [see preceding discussion]) inhibits agonist-stimulated $PIP_2$ hydrolysis in some cell types but not others (16). Indeed, functionally distinct G proteins may even selectively couple different receptors to $PIP_2$ hydrolysis in the same cell (18). Studies using *Xenopus* oocytes (large frog eggs frequently used in transfection studies) suggest that $G_o$ rather than $G_i$ may represent the pertussis-toxin-sensitive "$G_p$," at least in certain cell types (16). The identification of a novel G protein termed "$G_z$," which is not a substrate for ribosylation by either cholera toxin or pertussis toxin, has led to the proposal that $G_z$ may represent the "$G_p$" in a variety of tissues, including brain (where it is abundant) and platelets (19). More recently, however, several groups have purified and cloned members of a novel, ubiquitously distributed family of G proteins known as $G_q$. The α subunits of this family, including $\alpha_q$ and $\alpha_{11}$, have unequivocally been shown to stimulate phospholipase C, making them leading candidates for the heretofore elusive G proteins coupled to stimulation of phospholipase C in a pertussis-insensitive manner (12). Similar to the dual regulation of adenylyl cyclase, a number of receptors appear to inhibit phosphoinositide turnover, including receptors for adenosine, dopamine, 5-HT, and glutamate (20). In addition, evidence has accumulated that similar to the regulation of phospholipase C, G proteins may couple various receptors to phosphatidylcholine by means of phospholipase D (21). The existence of this signal transduction pathway has generated considerable interest, since it provides a mechanistic explanation for the frequently reported temporal dissociation between production of diacylglycerol and $IP_3$ (21).

## G PROTEIN COUPLING OF RECEPTORS TO ION CHANNELS

It has become increasingly clear in recent years that a large number of ion channels are regulated both directly and indirectly by G proteins; at least 12 separate ion channels appear to be directly regulated (under cell free conditions) by G proteins (3, 22). In the CNS, a variety of receptors regulate neuronal $K^+$ conductances by means of pertussis-toxin-sensitive G proteins. Activation of these $K^+$ channels results in neuronal hyperpolarization and is an important element in the regulation of the neuronal firing rate (23). Although both $\alpha_i$ and $\alpha_o$ are able to activate inwardly rectifying $K^+$ currents in neurons, $\alpha_o$ is markedly more potent. This is of considerable interest since $\alpha_o$ can be said to be predominantly localized in the nervous system (24), where its major role may be to regulate ion channels. Indeed, the most abundant G protein in the brain is $G_o$, which comprises 0.5%–1.0% of the total membrane protein (24). Within the brain, $G_o$ has a heterogenous distribution; it is particularly rich in the hippocampus and frontal cortex but is also widely distributed in other areas of the brain (25). This distribution parallels that of protein kinase C (but not adenylyl cyclase) in the brain, leading to the suggestion that $G_o$ may represent the pertussis-toxin-sensitive "$G_p$" in the brain (25). In addition to regulating $K^+$ channels, G proteins (in particular, $G_o$) also directly modulate neuronal $Ca^{+2}$ channels (3, 22, 26, 27). Voltage-activated $Ca^{+2}$ channels are present throughout neurons and regulate a variety of cellular functions, including, of course, neurotransmitter release. A variety of neurotransmitter receptors (including $\alpha_2$-noradrenergic, $GABA_B$, and adenosine A1) inhibit neuronal voltage-sensitive $Ca^{+2}$ channels, and this receptor-stimulated modulation of $Ca^{+2}$ ion channels may be (at least in part) the molecular mechanism whereby nerve terminal autoreceptors inhibit neurotransmitter release (26, 27).

## REGULATION OF G PROTEINS BY HORMONES

The CNS is a major target for the actions of glucocorticoids, thyroid hormones, and gonadal hormones, but the biochemical alterations ultimately responsible for producing the effects remain unclear. Malbon et al. (28, 29) coined the term "permissive hormones" to describe agents such as glucocorticoids and thyroid hormones that modulate the actions of a variety of agents acting through cAMP. Increasing evidence suggests that these modulatory actions are exerted to a significant degree through G protein regulation. Thus, in vivo alterations of hormonal levels have been demonstrated to alter the steady-state levels of several G protein subunits and thereby regulate the overall sensitivity of transmembrane signaling in a variety of peripheral tissues (30–32). Less information is available about the effects of hormonal manipulation on G protein regulation in the CNS. However, it has been demonstrated that 7-day administration of corticosterone increases the transcription and expression of $G\alpha_s$ while decreasing both the mRNA and immunoreactivity of $G\alpha_i$ in rat cerebral cortex (33). Moreover, adrenalectomy without corticosterone replacement results in a significant 20% decrease in $G\alpha_s$ mRNA, suggesting in vivo physiologic regulation (33). It has also been demonstrated that pretreatment of mouse striatal neurons in primary culture with 17 β-estradiol or testosterone increases the pertussis-toxin-catalyzed ADP-ribosylation of $G\alpha_o$ and/or $G\alpha_i$ subunits (34).

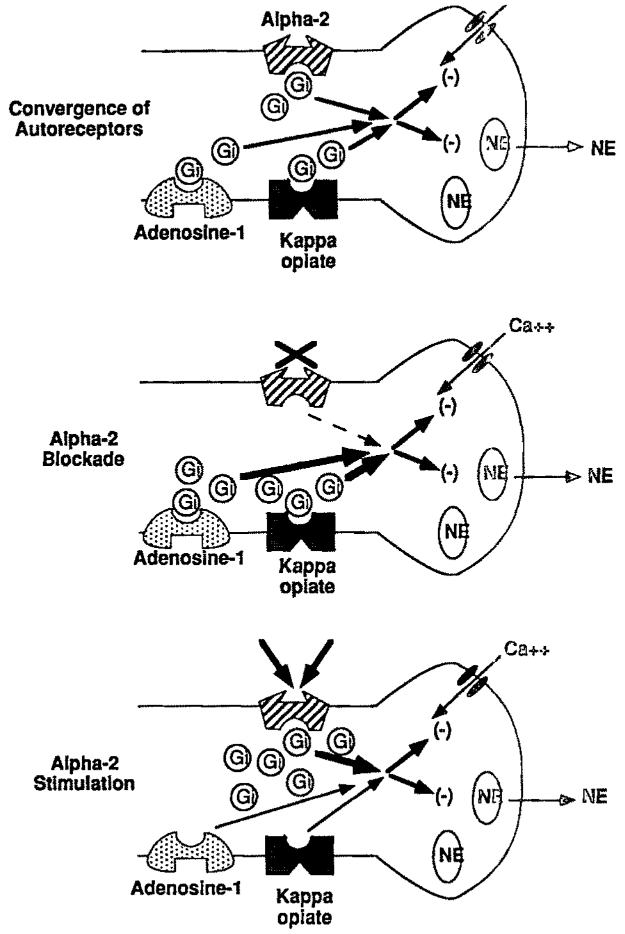
Abundant evidence supports an interaction between thyroid and adrenal hormones and psychiatric illness, particularly in affective disorders. Thus, primary disorders of both the thyroid and hypothalamic-pituitary-adrenal (HPA) axis have been linked with depressive, manic, and anxiety symptoms. Additionally, there is general agreement that more than 50% of patients with major depression exhibit hyperactivity of the HPA axis, as evidenced by hypercortisolemia, ACTH hypersecretion, and nonsuppression of plasma cortisol after dexamethasone administration (35). Similarly, at least some studies have shown the administration of thyroid hormones to be beneficial in the treatment of refractory depression and rapid-cycling bipolar disorder. Although a variety of biochemical effects may contribute to the CNS manifestations of abnormalities in thyroid or corticosteroid status, alterations of G protein function or content (with the inherent amplification of receptor responses) by these permissive hormones are an attractive mechanism. Similarly, the effects of gonadal hormones on G proteins, resulting in subsequent modification of signal transduction (34, 36), may be one mechanism by which biological maturation (puberty or menopause) triggers the expression of certain psychotic illnesses (e.g., schizophrenia in late adolescence, melancholic depression in late adulthood).

## G PROTEINS AS MEDIATORS OF NEUROTRANSMITTER-NEUROTRANSMITTER AND RECEPTOR-RECEPTOR INTERACTIONS

Most clinical studies in psychiatry, even when multiple measures are obtained, analyze data primarily in terms of independent measures, e.g., Is norepinephrine deficient? Is serotonin deficient? However, considerable preclinical evidence shows that monoamine systems interact, and a major question for neuroscience is emerging with regard to elucidating the mechanism(s) by which one neurotransmitter influences the response of a neuron to all the other converging afferent inputs.

The CNS is extremely complex, both anatomically and chemically, and there is a remarkable convergence of different receptors in common cortical layers (37) and a considerable convergence of neurotransmitter action (38). A single neuron in the brain receives thousands of synaptic inputs on the cell body and dendrites, and neuronal response is also modulated by a variety of hormonal and neurohormonal substances not dependent on synaptic organization. The neuron needs to integrate all the synaptic and nonsynaptic inputs impinging on it; this integration of a multitude of signals determines the ultimate excitability, firing pattern, and response characteristics of the neuron, and the neuron's response is then conveyed to succeeding targets by means of synaptic transmission. How does the single neuron decipher and integrate the multitude of signals it receives and, additionally, generate unique responses to each of these signals or combinations of signals? Not only do G proteins amplify signals, they also appear to form the basis of a complex information processing network in the plasma membrane (39). Thus, the ability of G proteins to interact with multiple receptors provides an elegant mechanism to organize the signals from these multiple receptors and to transmit them to a relatively much smaller number of effectors. Signals from a variety of receptors can be "weighted" according to their intrinsic ability to activate a given G protein and integrated to stimulate a single second messenger pathway. Similarly, the dual (positive and negative) regulation of adenylyl cyclase and perhaps of phospholipase C by G proteins allows stimulatory and inhibitory signals for these pathways to be balanced at the G protein level, yielding an integrated, dampened output (39). Convergence of a variety of neurotransmitters on the same ion channel has been demonstrated to occur in the locus coeruleus, hippocampus, thalamus, and substantia nigra (38, 40–43). Thus, it appears that a variety of receptors which coexist on neurons and mediate similar responses may share signal transduction mechanisms (38, 40, 43, 44). This convergence may occur at the level of the G protein or the effector itself. In both the cortex and the hippocampus, $\alpha_2$-adrenergic, adenosine $A_1$, and K-opiate receptors appear to compete for the same pool of G proteins to modulate $Ca^{+2}$ influx through voltage-sensitive $Ca^{+2}$ channels, thereby decreasing norepinephrine release (44–46). Additionally, there is mutual antagonism between these receptors with respect to modulating both $Ca^{+2}$ influx and norepinephrine release. That is, stimulating one of these receptors diminishes the effectiveness of the other receptors; this may be a mechanism for allowing neurons to "escape" from excessive inhibitory input (46) (see figure 2). Similarly, heterologous desensitization (a form of desensitization whereby exposure to a desensitizing agent leads to diminished responsiveness to a number of stimuli, apparently through postreceptor mechanisms) may be a compensatory mechanism designed to protect the neuron from the deleterious effects of overstimulation by multiple receptors. Thus, G proteins provide the first opportunity for signals from different receptors to be integrated; this complex web of interactions linking receptors, G proteins, and their effectors with signals converging to shared detectors appears to be crucial for the integrative functions performed by the CNS (39, 47, 48).

**FIGURE 2. Integration of Receptor-Receptor Interactions by a Common G Protein-Effector System**[a]

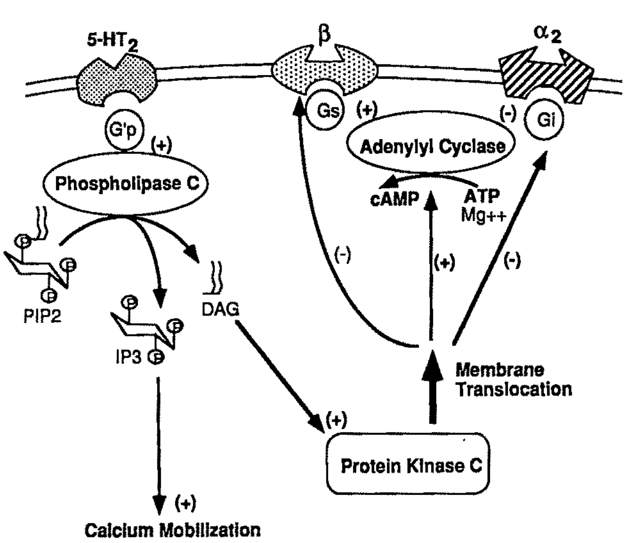


[a] Receptors that coexist on neurons and mediate similar responses may share signal transduction mechanisms. The top portion of the figure depicts a neuron with $\alpha_2$-adrenergic, adenosine $A_1$, and K-opiate receptors all converging onto a common pool of $G_i$-like proteins to inhibit $Ca^{2+}$ influx and norepinephrine (NE) release. Alpha-2-adrenergic antagonism increases the effectiveness of the other receptors (middle), possibly by making available a greater proportion of the shared G protein pool. In an analogous manner, stimulation of $\alpha_2$ receptors (bottom) diminishes the effectiveness of the other receptors through a disproportionate use of the common pool of G proteins. This may be a mechanism for allowing a neuron to "escape" from excessive inhibitory input.

## G PROTEINS AS MEDIATORS OF RECEPTOR-EFFECTOR CROSS-TALK IN THE CNS

In addition to their role as receptor-effector couplers, G proteins also serve as targets for regulating cross-talk between various second messenger systems. There are a number of potential sites of interaction of protein kinase C with the cAMP-generating system (49, 50; see figure 3). A large body of evidence suggests that phosphorylation of the β-adrenergic receptor by various kinases, including protein kinase C, desensitizes the receptor (50). Indeed, evidence suggests that the most commonly observed biochemical effect of antidepressants, namely, down-regulation of β-adrenergic receptors, may be mediated by cross-talk through protein kinase C (51, 52). Increasing evidence has also accumulated that the potentiating effects of protein kinase C on cAMP accumulation are mediated by $G_i$. Thus, in a number of cell types, including hepatocytes and striatal membranes (30, 53–55), activation of protein kinase C appears to

**FIGURE 3. Mediation of Receptor-Effector Cross-Talk in the CNS by G Proteins**[a]



[a] The figure depicts the complex intracellular cross-talk between receptors activating the phosphoinositide turnover pathway and receptors coupled to adenylyl cyclase. Receptor activation of phospholipase C results in the generation of $IP_3$ (IP3), which mobilizes $Ca^{+2}$ from intracellular stores, and diacylglycerol (DAG), which activates protein kinase C. There are a number of potential sites for the interaction of protein kinase C with the cAMP-generating system. Protein kinase C phosphorylates the β-adrenergic receptor, causing an uncoupling of the receptor from $G_s$. It also appears to phosphorylate adenylyl cyclase, resulting in an enhancement of adenylyl cyclase activity. Finally, at least in certain systems, it appears to phosphorylate and inactivate $G_i$, thereby removing its inhibitory tone. The net effect of the various potential interactions probably depends on differences among subtypes of G proteins and the relative abundance of protein kinase C isozymes.

enhance adenylyl cyclase activity by attenuating the inhibitory influence of $G_i$. Since the susceptibility of G proteins to be phosphorylated (and therefore regulated) by protein kinase C depends in large part on their conformational state (56), the degree of cross-talk is regulated by the relative degree of simultaneous stimulation of various receptors. In sum, it is clear that interactions between distinct second-messenger-generating systems represent a fine-tuning cellular network that regulates the neuron's reactions to the large number of extracellular signals it encounters. The net effect of the various potential interactions probably depends on the summation of the effects on individual components. In this context, quantitative and qualitative (e.g., conformation states) differences among subtypes of G proteins and the relative abundance of protein kinase C isozymes (57) in various cells may be major factors in determining the final integrated output.

## CLINICAL IMPLICATIONS

Given their widespread and crucial role in the integration, regulation, and amplification of signal transduction pathways, it is not surprising that abnormalities in the function and/or expression of various G proteins have been implicated in a variety of pathophysiologic states: pseudohypoparathyroidism type I, heart failure, certain endocrine tumors, McCune-Albright syndrome, diabetes, alcoholism, schizophrenia, mitral valve prolapse, chronic cocaine/opiate ingestion, aging, hypo/hyperthyroidism, and adrenalectomy/corticosteroid administration (58–81). It should be noted that G protein dysfunction appears to be the primary pathology in Albright's hereditary osteodystrophy, McCune-Albright syndrome, and endocrine tumors; in several of the other conditions, G protein abnormalities are probably secondary but are nonetheless implicated in the pathophysiology of the condition. I will briefly highlight some of the clinical conditions with well-characterized G protein dysfunction.

The first disease in which an intrinsic G protein abnormality was found is pseudohypoparathyroidism, so called because individuals with this condition have normal (or even higher than normal) levels of parathyroid hormone but have the manifestations of the disease because of cellular resistance to the hormone. In one form of the illness (Albright's hereditary osteodystrophy), the patients demonstrate a resistance to parathyroid hormone and to a number of hormones using cAMP as the second messenger. In these patients, lower than normal expression or function (approximately 50%) of $G\alpha_s$ has been demonstrated in cultured cells and in cells from freshly obtained tissue (58 and references therein). Additionally, distinct mutations have been identified in the gene encoding $G\alpha_s$ in different kindreds with the disease (58, 59), thereby providing the first demonstrations of an inherited mutation in a human G protein gene with important implications. The existence of more than one type of mutation resulting in abnormal function of $G\alpha_s$ demonstrates the genetic heterogeneity of this autosomal dominant disease. Moreover, the presence of an identical mutation in the $G\alpha_s$ gene, both in individuals with multiple hormone resistance and in those without hormone resistance, clearly suggests that $G_s$ deficiency is necessary but not sufficient for the full phenotypic expression of the disease (59). Thus, as has been suggested for a variety of psychiatric disorders, additional factors, including modifying genes and perhaps environmental factors, appear to be involved.

Studies have also demonstrated substantial abnormalities in G proteins in failing human and animal heart. A 50% lower than normal apparent concentration and function of $G_s$ in sarcolemma from a canine model of left ventricular failure has been reported. In contrast, end-stage idiopathic human congestive failure is associated with greater than normal activity of $G_i$, suggesting that various manipulations of $G_s/G_i$ stoichiometry may result in similar pathophysiology (60). Perhaps more akin to psychiatric research with respect to the use of peripheral blood cells to represent less accessible tissue (CNS, heart), one study (60) showed 80% lower than normal lymphocyte $G_s$ levels in subjects with congestive heart failure. More intriguing, successful treatment with captopril was associated with a significant two-fold increase in lymphocyte $G_s$ levels.

The following are summaries of research on the association of G proteins to psychiatric conditions.

### *Alcoholism*

The evidence for genetic factors in alcoholism is compelling (62), and, given the widespread medical, behavioral, and societal manifestations of this disorder, it is not surprising that there has been considerable research on biological factors that may predispose individuals to alcoholism. A variety of putative electrophysiologic, biochemical, and neuroendocrine markers have been studied, but increasing research has focused on G proteins not only as the mediators of the biochemical effects of alcohol but also as possible sites of underlying pathophysiology in individuals predisposed to the development of alcoholism (63).

Ethanol can profoundly affect the G protein-adenylyl cyclase signal transduction pathway (63). Chronic ethanol ingestion or in vitro exposure results in a desensitization of cAMP production in a variety of tissues, including brain (63, 64). The heterologous nature of desensitization of the adenylyl cyclase activity following chronic in vitro exposure of neuroblastoma cells to ethanol suggests a postreceptor (e.g., $G_s$) site. Chronic exposure of cultured cell lines to ethanol results in a more than 30% decrease in both the $\alpha_s$ protein and its mRNA (65, 66). In mice chronically fed ethanol, there is a reduction in the cholera-toxin-catalyzed [$^{32}$P]ADP-ribosylation of $G_s$ and a reduction of high-affinity [$^3$H]forskolin binding (which is thought to reflect binding to the complex of $\alpha_s$ and adenylyl cyclase) (63).

Clinical studies have also implicated $G_s$-adenylyl cyclase as a putative marker in alcoholism. One study showed that basal and adenosine-receptor-stimulated cAMP levels in fresh lymphocytes of alcoholic subjects were 75% lower than those of normal subjects or subjects with nonalcoholic liver disease (67). Cultured lymphocytes from alcoholics, grown in the absence of alcohol, also show some abnormalities in the cAMP signal transduction pathway (64). Similarly, platelet membranes of alcoholics reportedly abstinent from alcohol for 12–48 months demonstrate lower receptor- and $G_s$-stimulated adenylyl cyclase activity than do platelet membranes of age- and sex-matched comparison subjects (68). These findings suggest that low platelet adenylyl cyclase activity may be a genetic marker in alcoholics; this finding is supported by studies by my colleagues and me of cholera- and pertussis-toxin-catalyzed [$^{32}$P]ADP-ribosylation of platelet $G_s$ and $G_i$, respectively, in platelet membranes from abstinent alcoholics, subjects with concomitant diagnoses of major depression and alcoholism (major depression as the primary diagnosis), and age- and sex-matched comparison subjects. We observed significantly less $^{32}$P-labeling of $G_s$ (but not $G_i$) in the alcoholic group than in the comparison subjects. These findings are entirely consistent with the platelet adenylyl cyclase findings by Tabakoff et al. already described (68).

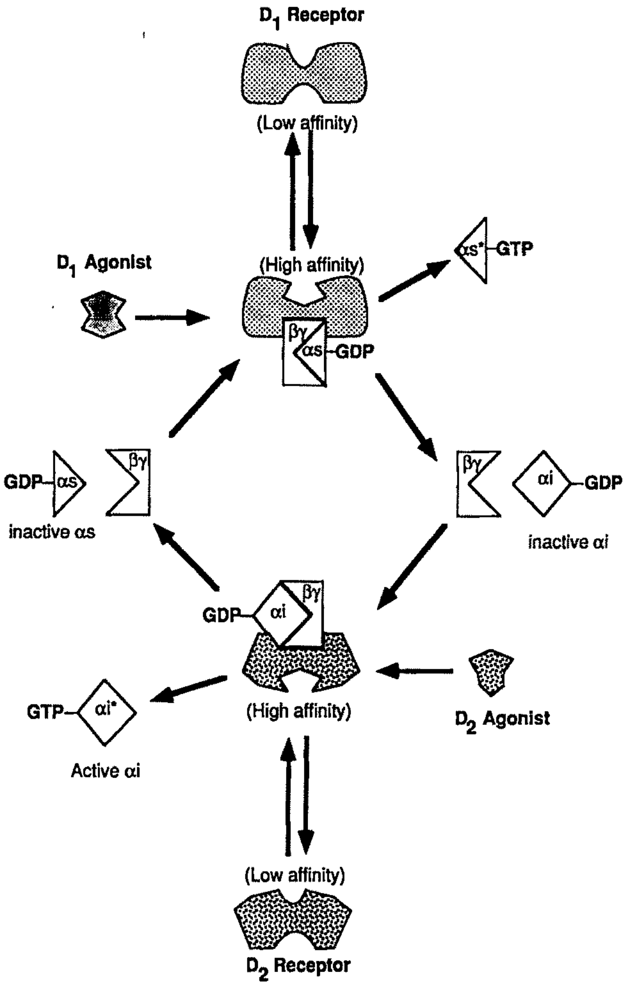
### *Chronic Opiate/Cocaine Use*

To my knowledge, there have been no clinical studies of the effects of acute or chronic opiate or cocaine ingestion on G proteins. Nevertheless, considerable preclinical evidence suggests that these substances exert at least some of their chronic effects (e.g., tolerance, dependence, withdrawal) through G proteins. A variety of opiate receptors are coupled to their effectors by G proteins, and pertussis toxin uncouples opiate receptors from the inhibition of adenylyl cyclase in cultured cells and in locus coeruleus neurons (3). Studies have shown that alterations in G protein levels are temporally correlated with neuronal activity in the locus coeruleus (more firing) and with the behavioral manifestations of the morphine withdrawal syndrome in rats (69, 70). These results suggest that alterations in the levels of G proteins may underlie the enhancement of neuronal excitability (and possibly withdrawal symptoms) observed after abrupt opiate discontinuation. In vitro studies of cultured neurons from rat spinal cord dorsal root ganglia have demonstrated that exposure to K-opiate agonists is accompanied by a 60%–70% decrease in levels of $\alpha_i$, in the absence of alterations in levels of $\alpha$, $\alpha_o$, and $\beta$ subunits (71), thereby providing a mechanistic explanation for opiate-induced heterologous desensitization. In contrast to the studies on opiates, only one recent study has directly examined cocaine's effects on G proteins, demonstrating low levels of $\alpha_i$ and $\alpha_o$ in the ventral tegmental area, nucleus accumbens, and locus coeruleus in rat brain after chronic cocaine use (72).

### *Schizophrenia*

Several years ago, studies using post-mortem human brain tissue demonstrated a greater response of adenylyl cyclase activity to fluoride stimulation (presumably acting through $G_s$) in the caudate and accumbens of schizophrenic patients than in the corresponding brain areas of comparison subjects (73). These studies suggested that a postreceptor defect may contribute to the presumed dopaminergic hyperactivity in schizophrenia, but it was several more years before they received additional, more direct support. Seeman et al. (74) used radioligand binding studies to explore the $D_1$-$D_2$ link in post-mortem human brain tissues. They proposed that the $D_1$ receptor may modulate ligand binding to the $D_2$ receptor by modifying the levels of G protein subunits ($\beta\gamma$) that these receptors share (see figure 4), and they reported that the $D_1$-$D_2$ link was missing in more than 50% of tissue samples from patients with schizophrenia and Huntington's disease, a finding apparently not due to prior neuroleptic use. In a study that examined G protein levels in post-mortem schizophrenic brains more directly, pertussis-toxin-catalyzed ribosylation in the left putamen was 42% lower in schizophrenic patients than in comparison subjects (75). These findings (suggesting low $G_i$ and/or $G_o$) would, of course, be compatible with enhanced dopamine-adenylyl cyclase function. In keeping with these lateralized abnormali-

**FIGURE 4. Reciprocal Modulation of Receptor Affinity by G Proteins**[a]



[a]The relative interchangeability of $\beta\gamma$ subunits allows further interaction of G proteins. When receptors coexist on neurons, a potential mechanism for modulation of receptor affinity by other receptors exists. Binding of an agonist to a receptor (e.g., $D_1$ receptor) promotes the dissociation of the G protein into $\alpha$ and $\beta\gamma$ subunits. The $\beta\gamma$ units thus released may drive the equilibrium for another G protein (e.g., $G_i$) toward the undissociated state and thereby modulate receptor affinity (in this case, the $D_2$ receptor). This may be one mechanism for the observed synergism between the $D_1$ and $D_2$ receptors despite opposite effects on adenylyl cyclase.

ties in postreceptor pathways in schizophrenic patients, greater than normal high-affinity [$^3$H]forskolin binding has been found in the left parahippocampal gyrus and CA1 region in post-mortem brains of schizophrenic patients (76). Since high-affinity [$^3$H]forskolin binding is thought to reflect binding to the complex of $\alpha_s$ and adenylyl cyclase, higher than normal levels of $\alpha_s$ and/or adenylyl cyclase would be the simplest explanation for these results. However, low levels of $G_i$ $\beta\gamma$ subunits would also result in a greater availability of free $\alpha_s$ to interact with adenylyl cyclase. Indeed, although this suggestion is highly speculative, a low level of $\beta\gamma$ subunits would be compatible with the higher than normal adenylyl cyclase activity (73), lower pertussis toxin ribosylation of $G_i/G_o$ (73) (since there would be fewer $\beta\gamma$ subunits available to form $\alpha\beta\gamma$ heterotrimers—the substrate for the ribosylation reaction), minimal or absent $D_1$-$D_2$ link (74), and greater [$^3$H]forskolin binding in post-mortem tissue from schizophrenic subjects (76).

### *Affective Disorders*

Two studies have directly examined G proteins in affective disorders. Young et al. (82) reported that the levels of $G\alpha_s$ in post-mortem brain tissue from manic-depressive subjects were significantly higher than those of comparison subjects. These findings are intriguing since they parallel those of Schreiber et al. (83), who reported "hyperfunctional" G proteins in manic subjects as determined by isoproterenol-stimulated [$^3$H]-GTPγS binding in leukocytes. Although these findings need to be replicated, they are exciting since lithium is reported to *attenuate* G protein function (see later discussion). Although a number of studies have demonstrated abnormalities in lymphocyte β-adrenergic receptor sensitivity and platelet $\alpha_2$-adrenergic receptor sensitivity in depressed patients (reviewed in reference 84), these abnormalities are difficult to interpret given the extensive literature documenting abnormalities in circulating catecholamines and glucocorticoids in depression. For example, significantly lower lymphocyte isoproterenol-stimulated cAMP accumulation was observed only in a subgroup of depressed patients with psychomotor agitation (and presumably high circulating catecholamine levels) (85). Similarly, a significant correlation between terminal insomnia and blunted lymphocyte cAMP accumulation in depressed patients has been observed (86). Additionally, my colleagues and I have demonstrated correlations between urinary measures of norepinephrine release and basal and postreceptor-stimulated adenylyl cyclase activity in both lymphocytes and platelets (unpublished observations). It is presently unclear whether these abnormalities in receptor and postreceptor sensitivity are primary or are the sequelae of abnormalities in circulating levels of catecholamines and/or stress hormones. Thus, studies of cultured cells from these patient populations are clearly needed to examine possible G protein defects free of the confounding effects of circulating catecholamines and hormones. Similarly, a common postreceptor abnormality (e.g., at the level of G proteins) would provide a mechanism for depressed patients' blunted growth hormone and prolactin responses to a variety of provocative challenges (35), but such an abnormality remains to be established.

### *Other Neuropsychiatric Conditions*

Lower than normal levels of platelet basal and postreceptor-stimulated adenylyl cyclase activity have been reported in both panic disorder (87) and posttraumatic stress disorder (88). Once again, one is faced with the possibility that these platelet abnormalities are secondary to abnormalities in plasma catecholamines and/or stress hormones. Another illness with a constellation of symptoms in common with panic disorder is a form of hyperadrenergic dysautonomia associated with mitral valve prolapse (77). Elegant reconstitution studies have recently demonstrated that upon reconstitution into cyc$^-$ lymphoma cells, erythrocyte $G_s$ from patients with mitral valve prolapse is hyperresponsive with respect to both adenylyl cyclase activation and receptor coupling (78). If a similar $G_s$ abnormality is present centrally in panic disorder, it would provide an attractive mechanistic explanation (i.e., desensitization of β-adrenergic-receptor-coupled adenylyl cyclase) for the therapeutic efficacy of both tricyclic antidepressants and monoamine oxidase inhibitors in this condition.

Finally, abnormalities in G proteins have also been implicated in Huntington's disease (79), Alzheimer's disease (80), and aging (81).

## G PROTEINS AS TARGETS OF PSYCHOTROPIC DRUGS

### *Lithium*

Although lithium is widely used for the treatment of recurrent affective disorders, the biochemical basis for its mood-stabilizing actions remains unknown. However, accumulating evidence suggests that lithium exerts substantial effects on second-messenger-generating systems. The discovery that lithium, at therapeutically relevant concentrations, inhibits the activity of the enzyme inositol-1-phosphatase (89, 90) has resulted in extensive research on the phosphatidylinositol signal transduction system and the generation of the inositol depletion hypothesis (since inositol does not cross the blood-brain barrier, lithium inhibition of inositol-1-phosphatase could deplete inositol and reduce phosphoinositide turnover) (91, 92). This hypothesis has been called into question, however, since alterations in brain $PIP_2$ levels have not been consistently found after lithium treatment (see 92). There has also been extensive research on lithium's effects on neuronal adenylyl cyclase. In rat brain preparations, both in vitro and ex vivo (i.e., after chronic treatment of the animal), lithium has been shown to attenuate receptor- and postreceptor-stimulated [GTP, Gpp(NH)p, fluoride, forskolin] adenylyl cyclase (93–96). In contrast to most antidepressants, lithium has been reported to induce few, if any, changes in the density of rat brain β-adrenergic receptors. Lithium also attenuates receptor-stimulated phosphoinositide turnover in rat brain and in human platelets (reviewed in references 92 and 96). Since lithium affects both phosphoinositide turnover and adenylyl cyclase, recent attention has focused on mechanisms shared by these two signal transduction systems, namely, G proteins. In this context, lithium has been reported to markedly attenuate the agonist-induced increase in [$^3$H]GTP binding in response to both isoproterenol and carbachol (97). Using a similar method, Schreiber et al. (83) observed greater isoproterenol-induced [$^3$H]GTPγS binding in leukocytes from untreated manic patients than in normal subjects or euthymic bipolar patients stabilized with lithium. In renal epithelial cells, lithium delays activation of adenylyl cyclase by Gpp(NH)p, which is compatible with attenuation of the formation of the active Gpp(NH)p-$\alpha_s$ subunit (98). Similarly, the inhibitory effects of chronic lithium use on rat brain adenylyl cyclase are reversed by increasing concentrations of GTP (93, 94). Taken together, these results suggest that the physiologically relevant effects of lithium on adenylyl cyclase may be exerted at the level of G proteins (presumably at a GTP-responsive step).

My colleagues and I have recently demonstrated significant increases in basal and postreceptor stimulated adenylyl cyclase activity in platelets (but not lymphocytes) obtained from normal volunteers after 14 days of lithium administration (95, 96). Since inactivation of $G_i$ appears to exert significant effects on adenylyl cyclase activity in platelets but not in lymphocytes (96), we postulated that the striking tissue-specific effects could be explained by a lithium-induced attenuation of $G_i$ function. To examine this more directly, we used platelet membranes from these same subjects to quantitate G proteins by using specific antibodies and toxin-catalyzed [$^{32}$P]ADP-ribosylation. We did not observe any abnormalities in immunolabeling of platelet $G_i$ but did observe a significant 37% increase in pertussis-toxin-catalyzed [$^{32}$P]ADP-ribosylation of platelet $G_i$. Since the undissociated, inactive αβγ heterotrimeric form of $G_i$ is the substrate for pertussis toxin, our results suggest that lithium inactivates $G_i$ by stabilizing the inactive, undissociated conformation. Corroborating our human platelet findings, we have recently observed similar increases in pertussis-toxin-catalyzed [$^{32}$P]ADP-ribosylation in rat cortex after 4 weeks of lithium use but no alterations in the immunolabeling of $G_s$, $G_i$, or $G_o$. Similar findings have been reported by another laboratory (R.S. Jope, personal communication). The mechanism by which lithium may inactivate $G_i$ is currently under investigation and may involve competition with $Mg^{+2}$ or cross-talk with protein kinase C (99). Whatever the mechanism, by affecting G proteins and thus multiple signal transduction mechanisms (adenylyl cyclase, phosphoinositide turnover) common to many different neurotransmitters, lithium may be in a unique position to affect the functional balance between neurotransmitter systems. One might speculate that it is precisely this effect on the functional balance between interacting neurotransmitter systems that underlies lithium's mood-stabilizing effects.

### *Antidepressants*

Despite extensive research, the molecular mechanisms of action of antidepressant drugs have not been clearly established. The most commonly observed biochemical effect of most clinically effective antidepressant treatments is a reduction in the norepinephrine-stimulated production of cAMP (desensitization), usually (but not invariably) accompanied by a reduction in the number of β-adrenergic receptors (down-regulation) (100). This has generally been regarded as an adaptation to the elevation of intrasynaptic norepinephrine through presynaptic mechanisms (e.g., reuptake blockade or monoamine oxidase inhibition). However, a direct postsynaptic effect of these drugs has been suggested by the observations that chronic in vitro exposure of human fibroblasts (101) and C6 glioma cells (102, 103) to tricyclic antidepressants leads to β receptor down-regulation. Other investigators have attempted to examine the effects of antidepressants at the level of G proteins. Desipramine appears to cause a functional uncoupling of the β receptor from $G_s$ in rat cortex (104) and interferes with the high-affinity state breakdown and subsequent activation of adenylyl cyclase, perhaps by decreasing the affinity of $G_s$ for guanine nucleotides (103, 105). Okada et al. (106) reported that pertussis toxin treatment of rats overcomes desipramine-induced β receptor desensitization (as assessed by measurements of isoproterenol-stimulated adenylyl cyclase activity) without attenuating (in fact, promoting) desipramine-induced β receptor down-regulation. While these results may suggest that $G_i$ and/or $G_0$ are involved in desipramine's effects, it is equally plausible that the removal of the inhibitory tone by pertussis toxin simply masks desipramine's desensitizing effects.

In studies using high in vitro concentrations (50–300 μM), it has been demonstrated that a variety of antidepressants interfere with $G_s$ activation of adenylyl cyclase (107). Interestingly, greater inhibition was observed when the antidepressants were added before, rather than after, the addition of GTP; this finding is also compatible with an antidepressant-induced inhibition of G protein dissociation. However, given the high doses of antidepressants used, the physiologic relevance of these findings remains unclear. It was reported (in an abstract) that chronic administration of imipramine decreased the levels of $G\alpha_s$ immunolabeling, cholera toxin ADP-ribosylation, and $G\alpha_s$ mRNA in rat brain (108). These results are difficult to reconcile with the results of some (109–111) but not all (104, 112) studies, suggesting increased postreceptor-stimulated adenylyl cyclase activity in rat cortical membranes after administration of antidepressants. Nevertheless, it remains possible that antidepressants attenuate β-adrenergic-mediated activation of $G_s$, while enhancing the effects of agents operating by pathways independent of the β-adrenergic receptor.

Like most antidepressants, electroconvulsive shock (ECS) desensitizes the β-adrenergic-mediated adenylyl cyclase activity in rat cortex and hippocampus (100). Fewer studies have investigated the effects of repeated ECS on postreceptor sites. However, repeated ECS is reported to decrease both the agonist-induced $[^3H]$GTP (113) and $[^3H]$forskolin (114) binding in rat cortex. In a study using $[^{35}S]GTP\gamma S$ binding (115), repeated ECS was found to decrease binding in prefrontal cortex and hippocampus but to have no effect in the striatum and to increase $[^{35}S]GTP\gamma S$ binding in the amygdala.

## CONCLUSIONS

Signal transduction through specific receptors plays a central role in neuronal activation. Understanding the mechanisms by which the binding of a neurotransmitter to a receptor at the cell surface is translated into a biochemical (and ultimately a physiologic) effect has clearly come a long way in the past decade. In particular, there has been dramatic progress in defining both the structure and the function of the signal-transducing G protein family. The diversity of the G protein family continues to grow. The G proteins serve the critical role of first amplifying or attenuating extracellularly generated neuronal signals and then transmitting these integrated signals to effectors, thus forming the basis for a complex information processing network (39).

The finding that the amount of G protein in a given tissue is not static, but is under the influence of physiologic, pathophysiologic, and pharmacologic perturbations, has clear implications not only for research into the etiology of various psychiatric conditions but also for the development of better treatments. Abnormalities in G protein function have now been identified in the etiology/pathophysiology of a variety of medical diseases. With the exception of chronic alcohol exposure, opiate withdrawal, and perhaps schizophrenia/neuroleptic exposure, the evidence for postreceptor dysfunction in psychiatric disorders is currently less direct. Nevertheless, given the widespread, critical roles of G proteins in the regulation of neuronal function, it seems likely that future, more sophisticated studies will yield insights into the involvement of G proteins in the pathogenesis of various major psychiatric illnesses. These putative G protein abnormalities may be subtle but sufficient to modify G protein functioning in response to neurotransmitter changes, permissive hormones, or other environmental events or stressors. Finally, given the increasing evidence that the currently available psychotropic drugs affect G proteins, the development of novel drugs with primary G protein targets remains an exciting prospect for the future. Indeed, it is intriguing that a number of the currently available pharmacologic agents, although not developed as such, appear to modify physiologic events that are linked to G proteins. These include heparin derivatives (116), volatile anesthetics (117), and caffeine-like agents (118). It has also been demonstrated that a variety of cationic amphiphilic neuropeptides activate G proteins in a receptor-independent manner (119); they represent a novel class of agents (receptomimetics, rather than receptor agonists). Interestingly, tricyclic antidepressants are also cationic amphiphilic compounds (95, 120), so they too may adopt a membrane-spanning conformation to allow for an interaction with the guanine nucleotide binding site on the G protein. Recent reports have also identified a novel class of agents that serve as allosteric enhancers and stabilize the high-affinity agonist-preferring conformation of the adenosine $A_1$ receptor (121). This may be viewed as being analogous to the manner in which benzodiazepines potentiate GABA-ergic neurotransmission. Such agents have a built-in safety mechanism, since the maximal effect of the drug depends on the availability of the endogenous ligand. This may be one mechanism underlying the relative safety of benzodiazepines in overdose. Additionally, the use of such allosteric modulators may serve to effectively re-equilibrate dysregulated neuronal systems (which are likely to be involved in psychiatric disorders) without the commonly encountered phenomena of tachyphylaxis (receptor down-regulation) and supersensitivity. Finally, given the fact that the GTPase activity serves as a "clock," allowing the system to cycle at a fixed rate, it seems likely that molecular biologic techniques will lead to the development of agents that either stimulate or inhibit GTPase by altering its catalytic rate, thereby dampening or amplifying the hormonal signal (without constitutively activating the G protein).

Appendix 1 provides more specific information on methods for G protein research.

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## APPENDIX 1. Methods for Studying G Proteins in Clinical Populations

Several distinct and complementary approaches can be used to study G proteins in clinical populations. The range of techniques developed in recent years to study G protein interactions with both receptors and effectors is described in detail in an excellent review by Milligan (122); only a brief overview of clinically applicable methods is presented here. The simultaneous use of immunoblotting techniques with specific antisera and toxin-catalyzed ADP-ribosylation yields the greatest information about the quantity and conformational (and therefore functional) state of specific G proteins. Several groups of researchers have generated specific antisera against synthetic peptides corresponding to the predicted amino acid sequence of various G protein subunits.

The use of these specific antisera is clearly the method of choice for quantitating G protein subunits. Similarly, these peptide antibodies can be used as specific probes of G protein receptor-effector coupling. Thus, although human platelets contain $G_s$, $G_{i2}$, $G_{i3}$, $G_q$, and $G_z$, only $G_{i2}$ appears to functionally couple to the $\alpha_2$-adrenergic receptor and thereby mediate adenylyl cyclase inhibition (123). However, since these antisera recognize both the dissociated α subunits and the corresponding undissociated, heterotrimeric αβγ complex, they do not, when used alone, provide information about conformational changes occurring in the absence of quantitative changes. For this reason, pertussis and cholera toxin are invaluable adjunctive tools for investigating functional and structural aspects of various G proteins. By using [$^{32}$P]nicotinamide-adenine dinucleotide (NAD$^+$) and determining the transfer of its [$^{32}$P]ADP-ribose moiety to membrane components, it is possible to obtain information about functional aspects of the G protein. In such investigations, [$^{32}$P]ADP-ribosylation of membrane components can be used because both cholera and pertussis toxin preferentially catalyze the ADP-ribosylation of a given conformational state (dissociated/undissociated) of the G proteins. Cholera toxin is very effective in ADP-ribosylating $G_s$ in the activated, dissociated form. In contrast, only the inactive, undissociated form of the $G_i$ protein is ADP-ribosylated by pertussis toxin. Thus, abnormal susceptibility of the G proteins to toxin-catalyzed ADP-ribosylation has been shown to result from an abnormal conformational state and to correlate with abnormalities in relaying molecular signals from extracellular receptors to intracellular effectors (113). However, there are potential problems in the use of toxin-catalyzed ADP-ribosylation as a means of detecting and quantifying G proteins in various tissues. First, both cholera toxin and, in particular, pertussis toxin ribosylate more than one G protein. In some cases, it may be possible to separate the G protein α subunits electrophoretically. Second, [$^{32}$P]NAD+ can be degraded by endogenous NAD-glycohydrolases, thereby altering substrate availability. This potential problem can be overcome by including a large excess of cold NAD in the reaction mixture.

Another functional probe is the so-called reconstitution assay, in which the G protein from the tissue in question is extracted and used to restore deficient adenylyl cyclase activity. Thus, using membranes that lack a specific G protein but have the appropriate receptor(s) and effector(s) allows for the determination of the functional activity of a G protein. Cyc$^-$ variants of the S49 lymphoma cell line lack $G_s$ but possess β-adrenergic receptors and catalytic units of adenylyl cyclase (124). Thus, detergent extraction of $G_s$ from a donor membrane allows for the full reconstitution of β-adrenergic and GTP-dependent adenylyl cyclase activity in this cell line. Such reconstitution studies have been used to demonstrate $G_s$ abnormalities in pseudohypoparathyroidism (125, 126), heart failure (127), and mitral valve prolapse (78). At present, a "$G_i$ equivalent" of the cyc$^-$ S49 lymphoma does not exist. Although more cumbersome, such a model can be generated by treating appropriate membranes with pertussis toxin and then examining the effects of exogenous $G_i$ (122).

Certain pharmacologic agents allow for the dissection of the multicomponent receptor/G protein/effector system. For example, a comparison of the adenylyl cyclase activity in response to receptor agonists, fluoride and G protein analogues (which act at the G protein), forskolin (which acts at $G_s$ and the catalytic unit of adenylyl cyclase), and Mn$^{+2}$ (which directly stimulates adenylyl cyclase) may allow identification of abnormalities in receptor, G protein, and effector to be identified. Similarly, cholera toxin and pertussis toxin may be used as probes of the signal transduction pathway because of their ability to constitutively activate $G_s$ and to inactivate/uncouple $G_i$, respectively.

Finally, agonist-induced GTP binding, agonist-induced GDP release, and agonist-induced increase in GTPase activity should, in theory, serve as good indexes for G protein involvement in the receptor-effector coupling being studied. However, a number of practical problems exist. First, the inability of GTP or its analogues to enter intact cells across the plasma membrane necessitates the use of membrane preparations. Second, in a number of systems, the basal GTP binding and GTPase activity are high, perhaps because signal-transducing G proteins represent only one group of GTP binding and hydrolyzing proteins. Thus, in the majority of instances, the high nonspecific GTPase activities generate sufficient "noise" to preclude an accurate determination of receptor-mediated increases. This assay appears, however, to be more effective in the study of receptors linked to pertussis toxin G proteins (122), perhaps because of their greater abundance in the plasma membrane and their greater enzymatic capacity (128).

# Predicting Substance Use in Late Adolescence: Results From the Ontario Child Health Study Follow-Up

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*Objective: The purpose of this study was to evaluate the relationship between use of tobacco, alcohol, marijuana, and hard drugs (substance use) and psychiatric disorder in early adolescence and substance use in late adolescence. Method: Adolescents included in the study were identified by means of a household sampling frame and participated in the Ontario Child Health Study in 1983 and the follow-up in 1987. There were 726 12–16-year-olds (369 boys and 357 girls) in 1983 who had complete information in 1987. Data on substance use were collected from adolescents by using a structured, self-administered questionnaire. Data on psychiatric disorder were collected in 1983 from both adolescents and their parents by using problem checklists to assess conduct disorder, attention deficit disorder, and emotional disorder. Results: Prior substance use in 1983 was associated strongly with subsequent use in 1987. Among the psychiatric disorders assessed in 1983, only conduct disorder made an independent contribution to predicting use of marijuana (relative odds=3.46) and other hard drugs (relative odds=6.82) in 1987, after prior use of these substances and coexisting attention deficit and emotional disorders were controlled. Corresponding estimates of attributable risk (the expected contribution of exposure to conduct disorder to the development of substance use) were 5.7% and 11.1%, respectively. Conclusions: Although a statistically significant relationship existed between conduct disorder in early adolescence and use of marijuana and hard drugs in late adolescence, the potential is limited for preventing substance use in the general population by treating conduct disorder early on.*

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Information on the strength of association and temporal relationship between specific types of psychiatric disorder and substance use in adolescence is important to those concerned with issues of etiology and prevention. Such information may provide a basis for developing causal hypotheses to understand better the origins of substance use, which could lead to prevention programs. The high frequency of substance use in nonreferred adolescents indicates that the general population is an important subject pool for studying this issue (1).

Research from clinical settings frequently reports a large overlap between substance abuse and other psychiatric disorders in adolescents (2). In the general population, relatively little is known about this overlap and even less about the chronology of the relationship. The studies directly relevant to this question suggest that risks for drug and alcohol abuse are elevated

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among nonreferred young adults experiencing depression or anxiety (3, 4).

The research included in this report seeks to advance our understanding of the relationship between psychiatric disorder and substance use among adolescents in the general population. The specific objectives are 1) to describe the relationship between patterns of substance use in early versus late adolescence among a cohort enlisted as 12–16-year-olds, 2) to evaluate the strength of association between psychiatric disorder assessed in early adolescence and substance use reported in late adolescence, controlling for prior substance use and sex, and 3) to estimate the reduction in late substance use (attributable risk) that might be associated with effective (early) treatment of psychiatric disorder. Adolescents included in the study were identified by means of a household sampling frame and participated in the Ontario Child Health Study, an interview survey of 1,869 families with children aged 4 to 16 years in 1983. This article complements earlier ones (5, 6) that focused on the prevalence, patterns, and correlates of substance use among adolescents aged 12 to 16 years.

## METHOD

### Survey Design

Data for the analyses come from families who participated in the original Ontario Child Health Study in 1983 and the follow-up in 1987. The methodology used in the original study is described in detail elsewhere (7). Briefly, the target population of the Ontario Child Health Study included all children aged 4 to 16 years on Jan. 1, 1983, whose usual place of residence was a household dwelling in the province of Ontario. Children living on Indian reserves, in collective dwellings such as institutions, and in dwellings constructed since June 1, 1981 (census day), were excluded systematically from the survey but accounted for only 3.3% of the target population. The sampling frame (source of subjects) was the 1983 Canada census, with the sampling units being household dwellings. The sample was obtained by stratified, clustered, and random sampling from the census file.

Interviewers collected information from the female head of household (parent) and youth aged 12 to 16 during a home visit. The field work was done in January and February 1983 by Statistics Canada—responsible at the federal level for the census, labor force survey, and other data collection for government. Among all eligible households, 91.1% (N=1,869) participated.

### Sample

Eligible for the analyses in this article were adolescents aged 12 to 16 during the original Ontario Child Health Study in 1983 who were aged 16 to 20 during the follow-up in 1987. In 1983 there were 1,302 eligible adolescents in the age group who participated in the original Ontario Child Health Study. Data losses in 1983, attributable to refusal or incomplete subject response on the variables used here, reduced the sample eligible for analysis to 1,202. At follow-up in 1987, complete information was obtained on 60.4% (N=726 of 1,202) of eligible adolescents who had complete information in 1983. This group, consisting of 369 males and 357 females, formed the sample for the present study.

### Variables and Measurements

Both adolescent and parent (female head of household) responses were used in the analyses. Data were collected from adolescents by using structured, self-administered questionnaires completed at home in private by each participating youth aged 12 to 16. The Statistics Canada interviewer was available during the completion of the questionnaire to clarify wording, if required. To protect the rights of privacy of each youth, the completed questionnaire was placed in a Manila envelope, which was then sealed.

Data were collected from parents by using a structured, self-administered questionnaire nearly identical in form and content to the youth self-report. Anonymity of respondents was guaranteed. Numerical codes and record linkage were used to match questionnaires within households; household identities were withheld from the investigators. The data collection procedures were the same in both 1983 and 1987.

Brief definitions of the variables used in the analyses along with test-retest reliability estimates of measurement are given in table 1. The time period for assessing all of the variables in table 1 was the 6-month period before data collection. Substance use was measured in 1983 and 1987 by using information collected from adolescents only. Psychiatric disorder was measured by using information collected in 1983 from both adolescents and parents. For measuring the individual psychiatric disorders, we developed scales comprised of problem behaviors (items) added together to form a score, which was converted to a binary rating to indicate the presence or absence of disorder. Items for the scales were selected from the Child Behavior Checklist (8) according to their ability to describe modified *DSM-III* criteria for each of the disorders. When too few items existed in the Child Behavior Checklist for satisfactory measurement, new items were generated to complete the scale. Scale items were included in checklists with versions for both parents and youth aged 12 to 16. An adolescent was classified with the disorders in table 1 on the basis of one (i.e., parent or youth self-report) or both (parent and youth self-report) scale scores reaching or exceeding prespecified thresholds. Adolescents had to have scale scores below threshold on both assessments (i.e., parent and youth self-report) to be classified as not having a disorder. Although our classifications should not be confused with clinical diagnoses, earlier evaluation of our methods of classification in a general population sample indicated that they provided a good

**TABLE 1. Definition of Questionnaire Variables and Test-Retest Reliabilities of Measurement in a Study of Substance Use in Late Adolescence**

| Respondent Variable[a] | Description | Test-Retest Reliability[b] % Agreement | Test-Retest Reliability[b] Kappa |
|---|---|---|---|
| Adolescent substance use in 1983 and 1987[c] | | | |
| Tobacco | Smoking of cigarettes or cigars every day for a continuous 30-day period or longer | 93 | 0.54 |
| Alcohol | Consumption of alcoholic beverages at least once a week for a continuous 4-week period or longer, and intoxication or consumption of at least two drinks on at least one of those occasions | 91 | 0.63 |
| Marijuana | Any use of marijuana or hashish | 99 | 0.91 |
| Hard drugs | Any use of amphetamines, stimulants, barbiturates, sedatives, tranquilizers, hallucinogens, psychodelics, heroin, or opiates | 97 | 0.72 |
| Psychiatric disorder in 1983[d] | | | |
| Conduct disorder | Physical violence against persons or property and violation of social norms | 96 | 0.71 |
| Attention deficit disorder | Inattention, impulsivity, and motor overactivity | 91 | 0.34 |
| Emotional disorder | Feelings of anxiety and depression | 93 | 0.56 |

[a] All variables refer to the 6-month period before data collection.

[b] 1- to 3-month test-retest reliability (N=146).

[c] Adolescent report only.

[d] Adolescent and parent report.

approximation to corresponding clinical diagnoses made by child psychiatrists (7).

Estimates of test-retest reliability over a 1–3-month period were obtained in a more recent study for our measures of both substance use and psychiatric disorder. Table 1 displays percent agreement and coefficient kappa—a chance-corrected measure of agreement (9). Percent agreement exceeded 90 for all measurements. Coefficient kappa exceeded 0.50 for all measurements except attention deficit disorder, which was 0.34. (Details of this recent, unpublished study can be obtained from the authors.)

### *Statistical Analyses*

The relationship between patterns of substance use in early versus late adolescence was evaluated descriptively in a contingency table by characterizing changes in the pattern of use from 1983 to 1987. Substance use in 1983 was defined by using a 4-point cumulative scale (Guttman scale) that had the following categories: 1) no substance use, 2) tobacco and/or alcohol used, 3) tobacco and/or alcohol used *and* marijuana used, and 4) tobacco and/or alcohol used *and* marijuana used *and* hard drugs used. Substance use in 1987 was defined in precisely the same way. Only those adolescents whose responses conformed to a true cumulative scale in both 1983 and 1987 were included in this analysis.

Strength of association between psychiatric disorder in early adolescence (1983) and substance use in late adolescence (1987) was evaluated by using relative odds. Relative odds index the likelihood of an outcome in the presence compared to the absence of a predictor variable and were computed from logistic regression analyses. Only the independent contribution of each predictor variable is estimated by the relative odds in a logistic regression—the procedure makes statistical adjustments for all other predictor variables in the model. One logistic regression model was specified for each type of substance used in 1987: tobacco, alcohol, marijuana, and hard drugs. The following variables were defined as present or absent and were included in each logistic regression model: male child, use of same substance in 1983, conduct disorder, attention deficit disorder, and emotional disorder.

The psychiatric disorders that exhibited statistically significant relationships with substance use in the logistic regression analyses were retained for stratified analyses. These were done to assess the relative importance of disorder for assessing prognosis (usefulness in predicting the continuation of substance use) versus risk (usefulness in predicting the initiation of substance use). Psychiatric disorders that predicted initiation of substance use in 1987 (among nonsubstance users in 1983) were examined from the perspective of attributable risk. Attributable risk quantifies the expected contribution of an exposure to the development of new cases and is a measure of the maximum percent reduction in new cases (new substance users in the present context) that could be expected by eliminating the effects of exposure (disorder in the present context). Attributable risk is a function of strength of association—quantified here by the prevalence ratio (PR): percent of new substance users among exposed divided by the percent of new substance users among nonexposed, and the proportion of individuals exposed (p). The formula for the calculation is $[p\ (PR-1)] \div [p\ (PR-1) + 1]$.

## RESULTS

Table 2 shows the prevalences by sex for the variables used in the analyses. There were no differences between males and females in reported substance use except in

**TABLE 2. Prevalence of Substance Use and Psychiatric Disorder Among 726 Adolescents by Sex**

| Year and Characteristic | Males (N=369) |  | Females (N=357) |  |
|---|---|---|---|---|
|  | N | % | N | % |
| 1983 |  |  |  |  |
| Substance use |  |  |  |  |
| Tobacco, regular use | 33 | 8.9 | 36 | 10.1 |
| Alcohol, regular use | 26 | 7.0 | 18 | 5.0 |
| Marijuana | 27 | 7.3 | 27 | 7.6 |
| Hard drugs | 13 | 3.5 | 16 | 4.4 |
| Psychiatric disorder |  |  |  |  |
| Conduct disorder | 33 | 8.9[a] | 7 | 2.0 |
| Attention deficit disorder | 28 | 7.6[b] | 10 | 2.8 |
| Emotional disorder | 12 | 3.3 | 40 | 11.2[c] |
| 1987 substance use |  |  |  |  |
| Tobacco, regular use | 87 | 23.6 | 114 | 31.9[d] |
| Alcohol, regular use | 145 | 39.3 | 127 | 35.6 |
| Marijuana | 84 | 22.8 | 69 | 19.3 |
| Hard drugs | 33 | 8.9 | 39 | 10.9 |

[a] $\chi^2=16.99$, df=1, $p<0.001$.
[b] $\chi^2=8.38$, df=1, $p<0.01$.
[c] $\chi^2=17.26$, df=1, $p<0.001$.
[d] $\chi^2=6.33$, df=1, $p<0.05$.

1987, when more females (31.9%) than males (23.6%) reported tobacco use. In 1983, there were differences between males and females in the prevalences of psychiatric disorder. Males were classified more frequently with conduct disorder and attention deficit disorder, while females were classified more frequently with emotional disorder.

Table 3 shows the relationship between patterns of substance use in early versus late adolescence. Almost half of the adolescents who reported no substance use in 1983 were using substances in 1987. Among adolescents who reported use of tobacco and/or alcohol in 1983, only 18.9% reported no substance use in 1987, while 37.7% (22.6% plus 15.1%) reported use of substances at higher levels. Among adolescents who reported use of tobacco and/or alcohol and marijuana, 27.8% reported substance use at the same level in 1983, while the same percentage reported substance use at a higher level. Finally, among adolescents engaged in the use of all substances in 1983, 47.1% reported continued use at the same level.

The strength of association between sex, prior use of the same substance, and psychiatric disorder in 1983 and substance use in 1987 is quantified in table 4 by using relative odds. Being male was inversely related to tobacco use. Prior use of the same substance was related to subsequent use in all instances. Conduct disorder was associated with use of marijuana and hard drugs (relative odds=3.46 and 6.82, respectively) but not with use of tobacco and alcohol. The relative odds between attention deficit disorder and substance use and emotional disorder and substance use were all small (0.74 to 1.63) and statistically nonsignificant.

Table 5 shows the results of stratified analyses that examined the relative contributions made by assessments of conduct disorder in 1983 to predicting the continuation of (prognosis) and initiation into (risk) substance use in 1987. The data show that the predictive value (strength of association) between conduct disorder and use of marijuana in late adolescence was similar whether conduct disorder is used as a prognostic (prevalence ratio=2.00) or risk (prevalence ratio=2.20) indicator. The predictive value of conduct disorder was higher for use of hard drugs in late adolescence. If one assumes that conduct disorder is causal for initiation into use of marijuana and hard drugs, the attributable risk estimates suggest that reductions in the use of these substances of 5.7% (marijuana) to 11.1% (hard drugs) could be expected by effectively treating (removing the effects of) conduct disorder early on.

## DISCUSSION

Data from our research indicate that the transition from early to late adolescence in a cohort of 12–16-year-olds is marked by dramatic increases in the use of licit and illicit drugs. Although 87% (N=582 of 670) of 12–16-year-olds reported no substance use in 1983, only 54.3% of them reported no substance use 4 years later (table 3). The majority of adolescents who report early substance use will continue use in late adolescence. In particular, use of tobacco in early adolescence was a strong predictor of later use, with the relative odds in logistic regression reaching 11.01 (table 4).

Although prior use of the same substance is the strongest predictor of subsequent use, our data indicate that conduct disorder among 12–16-year-olds makes an independent contribution to predicting subsequent use of marijuana and hard drugs even after prior use of these substances and other psychiatric disorders is controlled. The predictive value of conduct disorder for subsequent use of marijuana and hard drugs is not unexpected. It confirms part of our earlier cross-sectional results in which conduct disorder was associated strongly with all categories of substance use (5) and is consistent with analyses based on both cross-sectional and prospective data that implicate behavioral deviance, delinquency, vandalism, aggression, and hostility in adolescent substance use in the general population (10–12). Although conduct disorder early on is associated with later use of marijuana and hard drugs, the reduction in substance use that might arise from effective treatment of early conduct disorder is limited. Our data indicate that the maximum reductions in use of these substances would be 5.7% (marijuana) and 11.1% (hard drugs). These reductions would only be realized if conduct disorder was causal for later substance use and the effects of exposure to conduct disorder were removed entirely by treatment. The size of attributable risk is constrained numerically by strength of association (relative risk) and frequency of exposure. In the present study, the frequencies of exposure to conduct disorder in 1983 among those not using marijuana or hard drugs (0.05 and 0.05, table 5) were relatively low; and the strengths of association between conduct

**TABLE 3. Changes in Substance Use Between 1983 and 1987 Among 12- to 16-Year-Olds**

| | Substance Use in 1987 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | | Tobacco and/or Alcohol | | Tobacco and/or Alcohol and Marijuana | | Tobacco and/or Alcohol and Marijuana and Hard Drugs | |
| Substance Use in 1983[a] | N | % | N | % | N | % | N | % |
| None (N=582) | 316 | 54.3 | 174 | 29.9 | 67 | 11.5 | 25 | 4.3 |
| Tobacco and/or alcohol (N=53) | 10 | 18.9 | 23 | 43.4 | 12 | 22.6 | 8 | 15.1 |
| Tobacco and/or alcohol and marijuana (N=18) | 2 | 11.1 | 6 | 33.3 | 5 | 27.8 | 5 | 27.8 |
| Tobacco and/or alcohol and marijuana and hard drugs (N=17) | 5 | 29.4 | 1 | 5.9 | 3 | 17.6 | 8 | 47.1 |

[a] A total of 670 (92%) of the 726 subjects in the sample reported patterns of substance use that conformed to a true Guttman scale, and only these respondents were included in the analyses above. Each row totals 100%.

disorder and use of marijuana and hard drugs were modest.

There is little evidence to indicate that attention deficit disorder will predict substance use when adjustments are made for overlapping conduct disorder (2, 5). It is noteworthy that a follow-up study of nonreferred children identified in the community as hyperactive and control subjects reported no differences of consequence in frequency of substance use at follow-up (13).

Our finding that the presence of emotional disorder at ages 12 to 16 does not predict substance use at ages 16 to 20 is unexpected in view of our earlier cross-sectional findings that saw a doubling or more of risk for substance use in adolescents classified with emotional disorder (5) and in view of other studies that reported excess prevalence of drug use in young adults who met criteria for depressive or anxiety disorders (3, 4). Differences in study methodology may explain the discrepancy. Our analyses here are based on data collected from a young cohort, prospectively, at two time points 4 years apart. Analyses from our previous study (5) were based on cross-sectional assessments of the same cohort, while analyses from the other two studies (3, 4) were based on retrospective reports collected from young adults. Data collected cross-sectionally and retrospectively are subject to more biases than data collected prospectively (14), and these could lead to inflated estimates of association. It is also possible that our measures of emotional disorder and substance use, being less detailed than the other two studies (3, 4), led to attenuations in strength of association. The value of emotional disorder in early adolescence (or more specifically defined depressive and anxiety disorders) for predicting substance use in the general population requires further study. It will be important in such studies to include measures of conduct disorder because of its strong relationship to substance use and potential to act as a confounder in the analyses.

The central issues in prospective studies focus on the adequacy of sampling design, participation, and measurement. Despite a powerful sampling design and high participation in 1983, 39.6% (N=476 of 1,202) of the sample was lost to follow-up in 1987. The contributing factors to sample loss in 1987 were inability to locate respondents, refusals among those found, and missing data in the responses given by those agreeing to participate. To evaluate this loss, respondents and nonrespondents in 1987 were stratified by conduct disorder (present versus absent) and use of marijuana and/or hard drugs (present versus absent) in 1983 (a total of four strata), and respondents were weighted to compensate for differential exclusions across the strata. (Details of the methodology are available elsewhere [15].) The attributable risks in table 5 were recomputed by using the weights applied to respondents to compensate for sample loss. The differences between the observed estimates in table 5 and the weighted estimates were minor. The observed versus weighted attributable risks for marijuana were 5.7% and 5.9%, and for use of hard drugs they were 11.1% and 12.5%. The higher weighted estimates suggest that sample loss has led to some weakening of the associations (conservative estimates).

The adequacy of our measures also deserves comment. Our classifications of psychiatric disorder are less detailed and specific than the structured interviews that are becoming available for epidemiologic research. Despite the lack of detail, it is noteworthy that our classi-

**TABLE 4. Relative Odds in Logistic Regressions for Adolescent Substance Use in 1987 by Sex, Previous Use of the Same Substance, and Psychiatric Disorder in 1983**

| | Substance Use in 1987 | | | |
|---|---|---|---|---|
| Characteristic in 1983 | Tobacco, Regular Use | Alcohol, Regular Use | Marijuana | Hard Drugs |
| Male | 0.65[a] | 1.10 | 1.14 | 0.59 |
| Same substance | 11.01[b] | 3.05[b] | 4.29[b] | 4.42[b] |
| Conduct disorder | 1.67 | 1.14 | 3.46[c] | 6.82[b] |
| Attention deficit disorder | 1.50 | 1.63 | 0.79 | 1.60 |
| Emotional disorder | 0.90 | 0.82 | 1.07 | 0.74 |

[a] $p<0.05$.
[b] $p<0.001$.
[c] $p<0.01$.

**TABLE 5. Prevalence of Use of Marijuana and Hard Drugs by Adolescents in 1987 by Use of Marijuana and Hard Drugs in 1983 and Presence or Absence of Conduct Disorder in 1983**

| Substance Use and Conduct Disorder | N | % | $\chi^2$ (df=1) | Proportion Exposed[a] | Prevalence Ratio | Attributable Risk (%) |
|---|---|---|---|---|---|---|
| Adolescents using marijuana in 1987 | | | | | | |
| Used marijuana in 1983 | | | | | | |
| Conduct disorder in 1983 | | | 4.29 | 0.17 | 2.00 | |
| Present (N=9) | 8 | 88.9 | | | | |
| Absent (N=45) | 20 | 44.4 | | | | |
| Did not use marijuana in 1983 | | | | | | |
| Conduct disorder in 1983 | | | 7.34 | 0.05 | 2.20 | 5.7 |
| Present (N=31) | 12 | 38.7 | | | | |
| Absent (N=641) | 113 | 17.6 | | | | |
| Adolescents using hard drugs in 1987 | | | | | | |
| Used hard drugs in 1983 | | | | | | |
| Conduct disorder in 1983 | | | 11.82 | 0.24 | | |
| Present (N=7) | 7 | 100.0 | | | | |
| Absent (N=22) | 4 | 18.2 | | | | |
| Did not use hard drugs in 1983 | | | | | | |
| Conduct disorder in 1983 | | | 12.54 | 0.05 | 3.50 | 11.1 |
| Present (N=33) | 9 | 27.3 | | | | |
| Absent (N=664) | 52 | 7.8 | | | | |

[a] Proportion in the group classified with conduct disorder in 1983.

fications of disorder achieve levels of (test-retest) reliability commensurate with or better than available structured interviews (16). Our measures of adolescent substance use also achieved acceptable reliability. Although there is no way to be sure that our adolescent respondents reported the truth about their substance use, precautions were taken to ensure confidentiality of the youth self-report, which we believe increased the likelihood of receiving accurate information.

Longitudinal or prospective studies offer two important advantages over cross-sectional surveys in studying the origins of adolescent substance use: they provide an opportunity to evaluate chronology in the relationships among variables, and they eliminate the problem of retrospective assessments that can be distorted by problems of recall and current circumstances. Results from our analyses are clear: 1) early substance use is a strong predictor of later substance use, regardless of type, 2) conduct disorder predicts use of marijuana and hard drugs even when statistical adjustments are made for prior use of these substances and coexisting attention deficit and emotional disorders, and 3) the potential for preventing substance use in late adolescence by treating conduct disorder early on is limited.

The strong relationship that we have observed between conduct disorder and substance use suggests that future research on the predictors of adolescent substance use should include measures of this disorder in their design. In addition, the effectiveness of mental health interventions with children and adolescents, particularly studies of conduct disorder, should be careful to include adequate measures of substance use even if these behaviors are not the object of interventions. Unfortunately, we cannot be too optimistic about the prospects of preventing substance use by treating conduct disorder in childhood. In the first place, we have not identified effective interventions with conduct disorder, although the search for them should be a priority (17, 18) and some promising treatments do exist (19). Second, even if effective treatment of conduct disorder is developed, the potential for preventing use of marijuana and hard drugs in late adolescence by treating children with conduct disorder is limited.

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## New Policy Regarding Letters to the Editor

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# A Note on Racial Bias in the Admission of Children and Adolescents to State Mental Health Facilities Versus Correctional Facilities in New York

Stuart L. Kaplan, M.D., and Joan Busner, Ph.D.

Objective: *In response to several studies suggesting that there is racial bias in the admission of proportionately more white children and adolescents to the child and adolescent mental health system than to the juvenile justice system, the authors tested whether white children and adolescents would be overrepresented compared with black children and adolescents in mental health facilities and underrepresented compared with black children and adolescents in juvenile correctional facilities when ethnic distribution in the general population was controlled.* Method: *Ethnicity, age, and sex of all white, black, and Hispanic 10–18-year-olds admitted in a 1-year period to facilities of the Office of Mental Health and facilities of the correctional system (the Division for Youth) of New York State were converted into rates per 100,000 population by using U.S. census data for the state. Admission rates per 100,000 population for ethnicity, age, sex, and source of referral were then compared in the two types of facilities.* Results: *There were no meaningful differences in population-corrected admission rates among black, white, and Hispanic children and adolescents in the state mental health system. In contrast, there was a vast preponderance of black children and adolescents admitted to the state juvenile correctional system. The systems have different points of entry: 100% of the juvenile justice admissions versus 17% of the mental health admissions were referred by the courts.* Conclusions: *Analysis of demographic variables failed to support an allegation of racial bias in admission to the child and adolescent public mental health system in New York State.*

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Lewis et al. (1, 2) concluded in two studies that racial bias on the part of the mental health system leads to the incarceration of black children and adolescents in juvenile offender facilities while white children and adolescents with similar symptoms are more likely to be hospitalized in psychiatric facilities. These studies have been influential (3). The methodology used in the first study consisted of clinical reports of incarcerated black delinquents with serious, unrecognized psychopathology (1). In the second study, which was data based, the proportion of black admissions to a juvenile correctional institution (67%) was significantly greater than the proportion of black admissions to a neighboring state mental health facility (29%) (2). In a series of multiple regression and discriminant function analyses, with psychiatric hospitalization or incarceration in a correctional facility as the dependent variables, race explained over 17% of the variance of admission to a correctional institution or mental health facility.

An additional study using a similar methodology by Westendorp et al. (4) lent support to the conclusions of Lewis et al. In Michigan, Westendorp et al. compared psychiatrically hospitalized adolescents at admission with incarcerated adolescents at admission on a number of measures and found that ethnicity and gender accounted for a substantial proportion of the variance in a discriminant function analysis. The proportion of black adolescents entering the juvenile justice system (36%) was significantly greater than the proportion of black adolescents entering the mental health system (4.5%).

To assess the degree to which racial bias might be operating in the New York State Office of Mental Health

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system, we gathered data by age, race, and sex on the inpatient population of the New York State Office of Mental Health children's psychiatric facilities and on inmates of the New York State juvenile justice system.

We hypothesized that black children and adolescents would be underrepresented compared with white children and adolescents in the mental health facilities and overrepresented compared with white children and adolescents in the juvenile correctional facilities when ethnic distribution in the general population was controlled. We also examined the relationships among age, sex, and ethnicity by institutional setting.

The methodology of our study with regard to ethnicity differed from that of the studies cited, which did not correct for the distribution of demographic variables in the general population. In contrast, we used U.S. census data to correct our results for the distribution of the demographic variables in the general population. In addition, we used an adequate sample size that included all admissions of children and adolescents to state psychiatric hospitals and correctional facilities over a 1-year period in an entire state.

Furthermore, our study focused on racial distribution within each system of care rather than comparing racial distribution between the two systems of care. Lewis et al. (1, 2) and Westendorp et al. (4) compared the racial distribution of mental health versus correctional systems. We hypothesized that the two systems of care are relatively independent and believed, therefore, that the relevant comparison groups were within the systems of care rather than between the systems of care. We tested the independence of the two systems by examining sources of admission to mental health and correctional facilities.

## METHOD

### *Settings*

The New York State Office of Mental Health operates six freestanding child psychiatric hospitals and nine psychiatric units for children and adolescents within New York State adult psychiatric hospitals. There are 731 psychiatric beds for children and adolescents operated under state auspices in New York. The beds are intended to provide longer-term psychiatric hospitalization for the more seriously emotionally disturbed children in the state. In addition, they often serve psychiatrically disturbed children whose needs cannot be met by social service agencies, county mental health agencies, or the private sector. They are most often used by the less affluent and less privileged.

The New York State Division for Youth, the juvenile correctional system, has 1,788 beds for children and adolescents between the ages of 8 and 18. Admission to Division for Youth facilities requires a hearing before a family court judge; the child or adolescent must be found guilty of violating the law and sentenced. There are several levels of restrictiveness in Division for Youth settings, ranging from open group home settings to locked, guarded, secure care settings.

### *Procedure*

To study differences in race, age, and sex distribution patterns in the facilities of the Office of Mental Health and the Division for Youth, we used the state's computerized databases to obtain the race, age, and sex of all 10–18-year-old white, black, and Hispanic children and adolescents admitted statewide in 1988 to inpatient Office of Mental Health facilities and to residential Division for Youth facilities. We did not include more than one admission of the same individual during the 1988 period; therefore, we have an unduplicated count.

To control for the distribution of ethnic categories in the general population, we obtained the distribution of ethnic categories by age and sex for New York State documented in the 1980 U.S. Census. The 1988 admission numbers for the Office of Mental Health and the Division for Youth were divided by the 1980 New York State population numbers for the respective ethnic category, age, and sex; the quotient was multiplied by 100,000.

## RESULTS

Before correcting for population rates, we found that 910 (62%) of the 1,474 Office of Mental Health admissions of children and adolescents 10–18 years old were white and only 341 (23%) were black; in contrast, 780 (56%) of the 1,405 Division for Youth admissions were black and only 389 (28%) were white. These ethnic proportions are in agreement with those of the earlier studies cited.

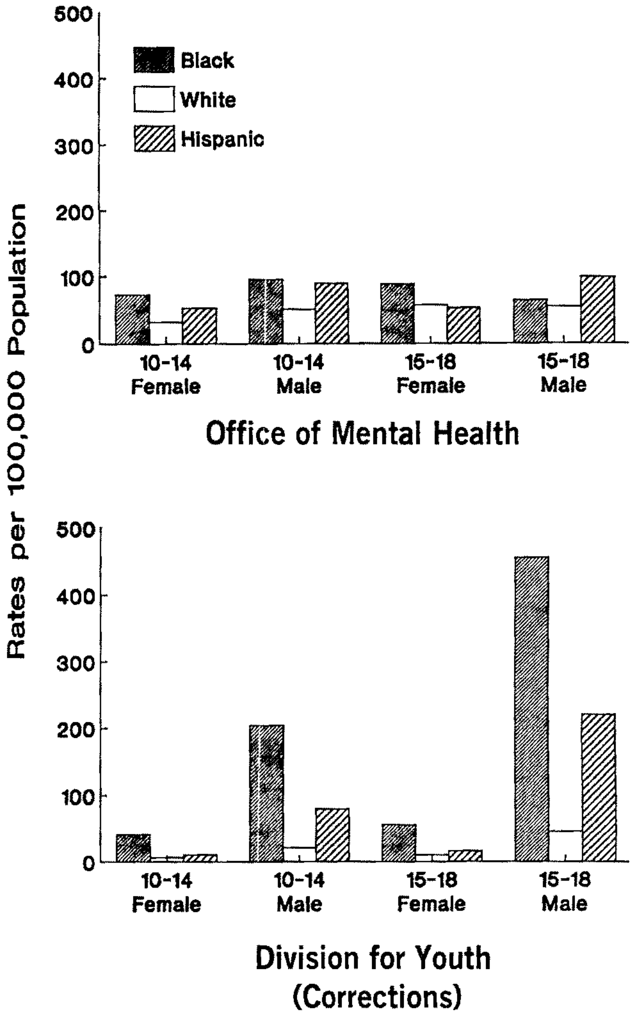
Figure 1 presents the data in rates per 100,000 population for each ethnic group, age, and sex. As shown, when corrected for population rates, there are large racial differences in Division for Youth facilities and only modest differences in Office of Mental Health facilities.

Twofold or greater differences in population-corrected admission rates are considered meaningful. As shown, when corrected for population distribution for age and sex, only the proportion of black to white 10–14-year-old girls admitted to Office of Mental Health facilities was greater than twofold. In contrast, for Division for Youth facilities, there were large ethnic differences at every age and sex category: there were seven times more black than white 10–14-year-old girls, over nine times more black than white 10–14-year-old boys, over five times more black than white 15–18-year-old girls, and over nine times more black than white 15–18-year-old boys.

When ethnic distribution in Office of Mental Health facilities was compared statistically with ethnic distribution in the general population by using goodness-of-fit chi-square analyses, there was a significant difference at each age and sex category: black children and adolescents were proportionately overrepresented compared with white children and adolescents. The same was true when ethnic distribution in Division for Youth facilities was compared with ethnic distribution in the general population (for 10–14-year-old girls, 10–14-year-old boys, 15–18-year-old girls, and 15–18-year-old boys, $\chi^2=39.0$, $\chi^2=41.6$, $\chi^2=14.6$, and $\chi^2=19.6$ for Office of Mental Health facilities and $\chi^2=99.2$, $\chi^2=553.2$, $\chi^2=98.3$, and $\chi^2=1156.8$ for Division for Youth facilities, respectively, df=2, $p<0.0001$ for all). Source of admission to the two agencies was examined. In 1988, all 1,405 of the black, white, and Hispanic 10–18-year-olds admitted to Division for Youth facilities came from the courts. In 1988, 246 (17%) of the 1,474 black, white, and Hispanic 10–18-year-olds admitted to Office of Mental Health facilities came from the courts. When we examined the ethnic distribution of the court admissions to Office of Mental Health facilities we found that 54 (22%) of the children were black, 163 (66%) were white, and 29 (12%) were Hispanic. This was significantly different from the ethnic distribution in the general population: there was a higher than expected proportion of black children and adolescents ($\chi^2=6.9$, df=2, $p<0.05$).

We also examined patient movement between agencies. In 1988 only 12 (0.8%) of the 1,474 children and adolescents admitted to Office of Mental Health facilities came from Division for Youth facilities. The racial breakdown of these youngsters (three [25%] were white, three [25%] were black, and six [50%] were Hispanic) significantly differs from that in the general population: white children and adolescents were significantly underrepresented ($\chi^2=19.3$, df=2, $p<0.0001$). None of the 1,405 youngsters admitted to Division for Youth facilities came from Office of Mental Health facilities.

FIGURE 1. Population-Corrected Comparisons of Ethnicity, Age, and Sex of Children and Adolescents Admitted to New York State Office of Mental Health and New York State Division for Youth Facilities in 1988



## DISCUSSION

That there were few meaningful differences between white and other ethnic categories in population-corrected admission rates in the New York State Office of Mental Health system for children and adolescents does not seem to support an allegation of racial bias for admission to this system. The conclusion that there is an apparent absence of racial bias in this mental health system depends on our understanding of the Office of Mental Health and the Division for Youth as independent. The excess of black children and adolescents in Division for Youth facilities compared with Office of Mental Health facilities is consistent with the findings of Lewis et al. (1, 2), although Westendorp et al. (4) found fewer black than white adolescents in correctional facilities. Had we analyzed our data as these authors did, our results would have been similar to theirs. Both Lewis et al. and Westendorp et al. compared ethnic categories between mental health and correctional facilities and concluded that black children and adolescents were overrepresented in correctional facilities and underrepresented in mental health facilities. In our data set, if we had considered the Division for Youth and Office of Mental Health systems as interrelated and had assumed that both systems provide care for similarly disordered children, we too would have concluded that black children were discriminated against by incarceration in Division for Youth facilities rather than admission to Office of Mental Health facilities. Our decision to examine data within each system rather than comparing data between the systems was based on our understanding that the two systems are largely independent.

For the most part, the juvenile correctional system and the mental health system in New York State have different points of entry. Children and adolescents enter the juvenile justice system exclusively through the courts. In contrast, children and adolescents enter the state mental health system from a variety of referral sources: private hospitals, school systems, and parental referral. Only in a modest percentage of cases (17%)

are youngsters referred by the courts to the mental health system. No children or adolescents were referred to the juvenile correctional system from the mental health system in 1988, and 0.8% were referred from the juvenile correctional system to the mental health system in 1988.

Because the two systems are largely independent, it seems appropriate to look for evidence of racial bias in mental health by examining the racial distribution within the mental health system. We found no statistical evidence of overrepresentation of white children and adolescents in the Office of Mental Health system. On the contrary, the results of the chi-square tests we computed suggest that black and Hispanic children and adolescents are admitted to Office of Mental Health facilities in excess of their distribution in the population. Because there are different points of entry to the mental health and juvenile justice systems, the entry of a disproportionate number of black children and adolescents to the juvenile justice system does not imply racial bias on the part of the mental health system.

To demonstrate an absence of racial bias in admissions to the Office of Mental Health system, many issues would have to be studied beyond the corrected rates of ethnic categories of individuals admitted to its facilities. Snowden and Cheung (5), in a discussion of the admission of adult ethnic minority groups to inpatient psychiatric care, discussed several variables related to the admission of adult psychiatric patients to psychiatric hospitals. These variables include the prevalence of psychiatric disorders in minority groups, the intensity of psychiatric symptoms in minority groups, help-seeking behaviors in minority groups, and gatekeepers' behavior. There is little knowledge of these matters with regard to child mental health.

In contrast to the Office of Mental Health, there was a dramatic preponderance of admissions of black compared with white children and adolescents in the Division for Youth population far beyond the distribution of black children and adolescents in the general population. The population-corrected ratio for black to white admissions to this system was almost 7:1. Reviewing the literature of official delinquency statistics indicates an approximate ratio of almost three black adolescents to one white adolescent (6, 7). The excess of blacks to whites in official delinquency statistics is the subject of considerable controversy in the sociology and penology literature as well as considerable sensitivity among the general public. There is no agreed upon explanation for these figures (8–12).

Our finding that there were more than twice as many incarcerations in the 15–18-year age range than in the 10–14-year age range corresponds roughly to the findings of many other studies on the prevalence of delinquency and age. In general, the studies support the idea that children who are delinquents at age 13 remain delinquent through age 18 and that the number of delinquents increases with age during adolescence. After age 18 or in early adulthood there is a decline in the number of delinquents or antisocial young adults (13–15). In addition, the disproportionate number of boys compared with girls admitted to Division for Youth facilities is consistent with the universal finding that male delinquents outnumber female delinquents. Although the ratio of male-to-female incarcerations in our data was 6.5:1, more sophisticated studies have found the ratio of male-to-female delinquents to range from 5:1 to 2:1 depending on the type of offense (16–18).

A separate but related issue to bias in admission to juvenile correctional institutions compared with mental health institutions is the prevalence of psychopathology in correctional facilities. Several studies have attempted to study the prevalence, severity, and type of pathology in juvenile correctional facilities (19–22). It seems clear that psychopathology is prevalent in such institutions, but, in New York State at least, because the two systems of care have different points of entry, this does not mean that the mental health system per se is racially biased.

Controlling for ethnic, age, and sex distribution in the general population and considering the degree of independence of the mental health and correctional systems allowed us to more adequately describe racial patterns of service utilization in the two systems of care.

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# Treatment of Tardive Dyskinesia With Vitamin E

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*Objective: Vitamin E (α-tocopherol), a free-radical scavenger, has been reported to improve symptoms of tardive dyskinesia. The authors attempted to replicate this finding under more controlled conditions in a larger study group. Method: Fifteen inpatients and six outpatients with tardive dyskinesia received up to 1600 IU/day of vitamin E for 6 weeks in a double-blind, placebo-controlled crossover study. Abnormal Involuntary Movement Scale (AIMS) examinations of these patients were videotaped and rated independently by two trained raters. Levels of neuroleptic medication and vitamin E were measured during both treatment periods. Eighteen patients who demonstrated high blood levels of vitamin E were included in the data analysis. Results: Vitamin E levels were significantly higher while the patients were receiving vitamin E than while they were receiving placebo. For all 18 patients, there were no significant differences between AIMS scores after receiving vitamin E and AIMS scores after receiving placebo. In agreement with previous studies, however, the nine patients who had had tardive dyskinesia for 5 years or less had significantly lower AIMS scores after receiving vitamin E than after receiving placebo. There were no changes in neuroleptic levels during vitamin E treatment. Conclusions: Vitamin E had a minor beneficial effect on tardive dyskinesia ratings in a selected group of patients who had had tardive dyskinesia for 5 years or less. This effect was not due to an increase in blood levels of neuroleptic medications.*

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Tardive dyskinesia is a movement disorder affecting up to 20% of patients treated chronically with neuroleptic agents (1, 2). A number of medications have been tried as therapies for tardive dyskinesia, but results have been mostly disappointing (3). Thus, tardive dyskinesia continues to be an important complication in the treatment of psychosis.

It has been proposed that tardive dyskinesia is due to neuroleptic-induced increases in free-radical production and the subsequent adverse effects of these free radicals on neuronal function (4). Long-term treatment with neuroleptic medication may result in a prolonged increase in dopamine turnover (5) and release (6). Dopamine is cytotoxic to some cell lines (7), an effect that may be mediated by free radicals (8–10). These highly reactive agents can produce membrane destabilization and protein oxidation (11). If the free-radical hypothesis is correct, antioxidants such as α-tocopherol (vitamin E) could inactivate these compounds (12) and exert therapeutic effects on tardive dyskinesia.

Two previous studies (13, 14) used high doses of vitamin E to treat patients with tardive dyskinesia and found improvement in up to 62% of patients. These patients had had tardive dyskinesia, on average, for relatively short periods of time (2.6 and 3.8 years, respectively). The larger study (13) found that the patients who improved had had tardive dyskinesia for a significantly shorter period of time than patients who did not improve. This effect of duration of tardive dyskinesia is consistent with a free-radical mechanism of cellular damage (15).

Although these reports are encouraging, replication studies are needed. Initial trials of a variety of other agents (e.g., choline and lecithin) demonstrated therapeutic effects that could not be replicated. The variable results of such trials may be due to methodological problems inherent in studies of tardive dyskinesia (16), including changes in neuroleptic blood levels, poor interrater reliability over time, stress-induced changes in severity of tardive dyskinesia, and natural fluctuations in the severity of tardive dyskinesia.

In this study, we attempted to control for some of these methodological problems. We administered up to 1600 IU of vitamin E to 21 patients using a double-blind, placebo-controlled, crossover design. Most of the

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subjects in the study (N=15) were inpatients for whom medication compliance was assured and extraneous stressors were relatively limited. All examinations of severity of tardive dyskinesia were videotaped and rated blindly at the conclusion of the study. To exclude the possibility that vitamin E reduces tardive dyskinesia simply by increasing neuroleptic levels, these levels were also monitored.

## METHOD

### *Patients*

Subjects were recruited from the inpatient wards and the outpatient clinic of an NIMH hospital and from a brief admissions program at a Veterans Administration (VA) hospital. The inclusion criteria were a diagnosis of tardive dyskinesia (17) for at least 6 months, age between 18 and 75 years, and the absence of serious medical or neurological illnesses. Candidates were excluded if there was evidence of substance or alcohol abuse within the previous 6 months. Patients were screened with a physical and neurological examination, routine blood and urine tests, electroencephalograms, and magnetic resonance imaging or computerized tomographic brain scans. Those with a family history of Huntington's disease were excluded.

Twenty-one candidates met these criteria and gave written informed consent. Their ratings of tardive dyskinesia severity (on the Abnormal Involuntary Movement Scale [AIMS] [18]) had been stable for at least 4 weeks before they entered the study. Psychiatric diagnoses were determined by Board-certified psychiatrists using *DSM-III-R* criteria. Demographic data, including duration of tardive dyskinesia, were gathered through personal interviews and chart reviews.

Patients were maintained on a constant, fixed oral dose of medication for at least 6 weeks before and during the study. One patient had received a long-acting injectable neuroleptic 6 weeks before entering the study and a second patient 10 weeks before entering the study; the remaining 19 patients had not received depot neuroleptics for at least 6 months.

### *Study Design*

Patients were assigned randomly to receive either vitamin E (10 patients) or placebo (11 patients) for the first 6 weeks of the 12-week, double-blind, crossover study. All patients took one 400-mg capsule four times daily. Vitamin E was administered according to the following schedule: 400 IU/day for week 1, 800 IU/day for week 2, 1200 IU/day for week 3, and 1600 IU/day for weeks 4–6. NIMH inpatients were rated weekly, and outpatients were seen at the beginning of the study and twice during each 6-week phase, for a total of 12 and five ratings, respectively.

Blood levels of medications were monitored at baseline and every 3 weeks. Vitamin E levels were measured by using fluorometry (Metpath Laboratories, Rockville, Md.). This method has a coefficient of variation of 10% (19). Levels of other medications were measured either by high-performance liquid chromatography or gas chromatography with ultraviolet electrodes (20, details available on request) when confounding peaks were present. The coefficients of variation for measurements of these medications ranged from 2.5% to 20%. The following tests were also performed every 3 weeks to monitor for adverse effects: prothrombin time, creatinine, creatine phosphokinase, thyroid indexes, cholesterol, and triglycerides.

### *Ratings*

Tardive dyskinesia was assessed by using a modified form of the AIMS rating scale (21). This modified form used separate ratings for choreoathetosis and dystonia. Separate ratings were also made for both left and right upper and lower extremities. Severity of movements was rated on a scale from 0 to 4 on which 0=no abnormal movements, 1=minimal abnormal movements that may be extremes of normal, 2=clearly abnormal movements, and 3 and 4=increasing severity and duration of movements. Seven body regions (described in the standard AIMS [18]) were rated for both choreoathetosis and dystonia. Two scores (right and left side) were given for the regions of upper and lower extremities. Thus, the highest possible total score for each type of movement was 36. The highest possible overall score was 72. Unlike the standard AIMS rating procedure, a point for severity was not subtracted if movements were greater with activation.

The standard AIMS examination (18) was performed during sessions that lasted approximately 5 minutes. All examinations were videotaped in the same room and at the same time of day each week. Most of the patients were also rated repeatedly for at least 4 weeks before entering the study to become familiar with videotaping. Meetings for establishing reliability were held every 1–3 weeks over the entire 3-year study period. All raters were blind to treatment with either placebo or vitamin E. At the completion of the study, videotaped AIMS examinations were reviewed by two blind raters. For these ratings, the intraclass correlation coefficient (ICC) (22) for total AIMS scores, based on 25 randomly selected ratings, was $r=0.82$ ($p=0.002$). Only AIMS scores of videotaped examinations were used for statistical analysis, except for one patient who refused to be videotaped. Live ratings were substituted for videotaped scores for this patient.

The patients' psychiatric status was assessed by using the Psychiatric Symptom Assessment Scale (23) and the Negative Symptom Rating Scale (24). These live ratings were performed the week before the patient entered the study (baseline) and again at the end of each 6-week treatment period by two trained raters. Using the ICC, we found that interrater reliability for the Psychiatric Symptom Assessment Scale was 0.72 ($p=0.002$) and for the Negative Symptom Rating Scale was $r=0.87$ ($p<0.001$).

### *Statistics*

Total AIMS scores from the end of the placebo and vitamin E phases were compared by using a one-tailed paired t test to test the hypothesis that vitamin E produced improvement. Total scores were derived by adding scores from all body areas for both choreoathetosis and dystonia. The patient group was divided in half on the basis of duration of tardive dyskinesia, and a separate comparison was performed on the half with the shorter duration (5 years or less). The duration of tardive dyskinesia of this group was similar to that of groups used in two previous studies of vitamin E (13, 14). A one-tailed paired t test was also used to compare the effect of vitamin E with that of placebo for this group. For these two comparisons, a p value of 0.025 was accepted as the criterion for statistical significance. These two comparisons tested the primary hypothesis of the study and were based on previous findings of improvement in subjects with shorter duration of tardive dyskinesia (15).

The possibility of a carryover or an order effect was tested by using Wilks's lambda. Additional comparisons of other variables were done by using two-tailed paired (unless otherwise stated) t tests. These included AIMS ratings subdivided by type of movement (choreoathetosis versus dystonia) or location (mouth, cheek, tongue, upper extremities, lower extremities, or trunk), Psychiatric Symptom Assessment Scale and Negative Symptom Rating Scale scores, and neuroleptic and other drug levels. Because a number of comparisons were made, a p value of 0.005 was accepted as significant for these additional tests. Pearson's correlation coefficients were used to determine apparent associations between patient variables and improvement with vitamin E. For a measure of improvement with vitamin E, AIMS scores after vitamin E were subtracted from AIMS scores after placebo.

## RESULTS

Fifteen subjects were inpatients and one was an outpatient at the NIMH hospital and clinic. Five were outpatients at the VA hospital. Three patients were not included in the data analysis: one dropped out and two had inconsistent vitamin E blood levels. No adverse effects were noted.

The diagnoses of the 18 subjects included in the final analysis are given in table 1. Six patients had a previous diagnosis of substance or alcohol abuse. The patients' mean age was 43.9 years (SD=2.8), and the mean duration of tardive dyskinesia was 5.9 years (SD=4.8). The mean total dystonia score was 5.5 (SD=0.5) at baseline, and the mean choreoathetosis score was 10.2 (SD=4.1). The mean overall severity score (item 8 on the AIMS) was 2.6 (SD=0.8) out of a possible 4. The 15 patients on neuroleptics were receiving an average dose of 1946 mg/day (chlorpromazine equivalents) (25, 26); three of these patients were receiving molindone (mean dose=4304 mg/day [chlorpromazine equivalents]) and 12 were receiving other agents (mean dose=1120 mg/day [chlorpromazine equivalents]). The mean neuroleptic levels of the 15 patients were 433 ng/ml (SD=822) (chlorpromazine equivalents) at baseline, 388 ng/ml (SD=670) while taking vitamin E, and 246 ng/ml (SD=258) while taking placebo. Other medications are listed in table 1. Doses of all medications were held constant.

There were no significant differences in blood levels of neuroleptics or other medications between the vitamin E and placebo phases. Furthermore, there were no correlations between neuroleptic levels and total AIMS scores or differences in AIMS scores (total AIMS score while receiving placebo minus total AIMS score while receiving vitamin E). Levels of vitamin E were significantly higher after the 6-week treatment period (35.0 mg/liter, SD=9.9) than at baseline (13.2 mg/liter, SD=3.6) or after placebo administration (13.6 mg/liter, SD=3.6) (paired t=–11.7, df=17, p=0.0001).

For all 18 patients, there were no significant differences between total AIMS scores after receiving vitamin E (mean=16.8, SD=6.5) and after receiving placebo (mean=17.3, SD=6.5) (t=–0.64, df=17, p=0.26). Similar results were found when scores were subdivided by type or location of involuntary movements. There was no main effect of the order of administration of vitamin E or placebo on total AIMS scores (F=0.17, df=1, 17, p=0.68). There was no correlation between improvement while receiving vitamin E and age or severity of tardive dyskinesia. Women demonstrated slightly more improvement than men while receiving vitamin E, but this difference was not significant at the 0.005 level (t=–2.68, df=16, p=0.02, unpaired t test).

To examine the effect of duration of tardive dyskinesia on treatment response, patients were divided in half on the basis of how long they had had tardive dyskinesia. One group had had tardive dyskinesia for more than 5 years and the other had had it for 5 years or less (5-year group). When results from the 5-year group were analyzed separately, the total AIMS scores after vitamin E administration (mean=12.8, SD=7) were 18.5% lower than the ratings after placebo administration (mean=15.7, SD=6.2) (t=–2.54, df=8, p<0.02). For the 5-year group, neither choreoathetotic nor dystonic movements showed significant improvement after vitamin E administration when analyzed separately (t=–2.08, df=8, p=0.06; t=–0.98, df=8, p=0.36, respectively). No significant differences were found with vitamin E treatment when subscores were examined by body region (orobuccolingual versus extremities and trunk). As with the total group, there was no carryover effect for the 5-year group (F=0.03, df=1, 8, p=0.87).

The 5-year group had a markedly shorter mean duration of tardive dyskinesia (2.3 years) than patients who had had tardive dyskinesia for more than 5 years (9.6 years). Both groups had similar elevations in vitamin E levels, and neither had significant changes in neuroleptic or other drug levels during either phase of the study.

**TABLE 1. Clinical Characteristics and Modified AIMS Scores of 18 Patients With Tardive Dyskinesia From Videotaped Ratings During 12-Week Crossover Study of Vitamin E and Placebo**

| Patient | Age (years) | Sex | Diagnosis | Duration of Tardive Dyskinesia (years) | Medications | First Treatment | AIMS Score | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | After Placebo | After Vitamin E |
| 1 | 55 | M | Schizotypal personality | 20 | None | Placebo | 25.5 | 28.0 |
| 2 | 48 | M | Schizophrenia, undifferentiated | 11 | Haloperidol, benztropine | Placebo | 19.0 | 20.0 |
| 3 | 48 | F | Bipolar disorder | 10 | Lithium, haloperidol, benztropine, carbamazepine | Vitamin E | 23.5 | 14.5 |
| 4 | 27 | M | Schizophrenia, undifferentiated | 9 | Mesoridazine, lithium, diphenhydramine, levothyroxine sodium | Vitamin E | 22.0 | 22.5 |
| 5 | 40 | M | Schizophrenia, paranoid | 9 | Lorazepam | Vitamin E | 23.5 | 31.5 |
| 6 | 33 | F | Schizophrenia, undifferentiated | 8 | Haloperidol, benztropine | Placebo | 17.0 | 22.0 |
| 7 | 42 | M | Schizophrenia, undifferentiated | 7 | Molindone, benztropine | Vitamin E | 7.5 | 10.5 |
| 8[a] | 71 | M | Bipolar disorder | 6 | Perphenazine, lithium, lorazepam | Placebo | 12.5 | 19.5 |
| 9[a] | 61 | M | Depression, psychotic | 6 | Lithium, fluoxetine, enalapril, sulfamethazine | Vitamin E | 25.5 | 20.0 |
| 10 | 64 | F | Schizophrenia, residual | 5 | Haloperidol, amantadine, triazolam, tolazamide | Vitamin E | 25.0 | 15.0 |
| 11 | 36 | F | Schizophrenia, undifferentiated | 4 | Haloperidol | Placebo | 20.5 | 14.5 |
| 12[a] | 43 | M | Schizoaffective disorder | 3 | Thioridazine, lorazepam, fluoxetine | Vitamin E | 8.0 | 7.0 |
| 13 | 28 | M | Schizophrenia, paranoid | 3 | Thioridazine, diazepam, carbamazepine | Vitamin E | 8.5 | 9.0 |
| 14 | 29 | F | Schizophrenia, undifferentiated | 2 | Haloperidol, trihexyphenidyl | Placebo | 23.0 | 18.5 |
| 15 | 33 | M | Schizophrenia, undifferentiated | 1 | Molindone, benztropine | Placebo | 12.5 | 13.0 |
| 16[a] | 39 | M | Bipolar disorder | 1 | Thiothixene, lithium, benztropine, propranolol | Vitamin E | 13.0 | 11.0 |
| 17[b] | 53 | M | Schizophrenia, undifferentiated | 1 | Fluphenazine, benztropine | Placebo | 13.0 | 11.0 |
| 18 | 41 | M | Schizophrenia, undifferentiated | 1 | Molindone, benztropine | Placebo | 18.0 | 16.5 |

[a] Outpatient.
[b] Live AIMS ratings.

There were no significant differences between Psychiatric Symptom Assessment Scale or Negative Symptom Rating Scale scores at the end of vitamin E treatment and after placebo treatment (t=0.55, df=13, p=0.59 and t=0.15, df=13, p=0.88, respectively).

## DISCUSSION

Vitamin E treatment was not effective in the group as a whole in lowering ratings of tardive dyskinesia. In contrast, two earlier reports (13, 14), which included patients with a shorter duration of tardive dyskinesia (averaging 2.6 and 3.8 years, respectively), did find improvement with vitamin E. For a similar comparison, we divided our patients into those with short-term (5 years or less) tardive dyskinesia and those with long-term (more than 5 years) tardive dyskinesia. The short-term group had significantly lower scores while receiving vitamin E than while receiving placebo, consistent with the previous studies. These data suggest that vitamin E may be somewhat effective early in the course of tardive dyskinesia.

The difference between vitamin E and placebo treatments was 18.5% in our short-term group. In comparison, the first controlled study (13) found a 45% improvement. The second report (14), similar to ours, found only a 21% improvement. The greater improvement seen in the first study compared with the latter two could be due to several methodological differences. The first study used live ratings and did not include measures of interrater reliability. The second study used ratings of videotaped examinations, as did our study. Ratings of videotapes may have the advantage of improved interrater reliability. The first study might also have been complicated by changes in neuroleptic doses or compliance problems, issues largely avoided in the present study.

The potential role of vitamin E in treating tardive dyskinesia remains unclear. The relatively minor 18.5%

improvement in the short-term group suggests that vitamin E has little clinical efficacy. Nevertheless, several patients appeared to improve markedly while taking vitamin E, a change not always reflected in AIMS ratings. For example, one patient with severe truncal dystonia was able to walk erect for the first time in 2 years during vitamin E treatment but continued to exhibit marked neck dystonia. His rating for truncal dystonia decreased from severe to moderate (from 4 to 3). This improvement was negated on the AIMS score by a less clinically important increase in choreoathetosis of the fingers. This suggests that even though improvement on vitamin E is not usually dramatic, some patients may show substantial clinical improvement.

It is unclear whether vitamin E, if used for prophylaxis, could prevent the development of tardive dyskinesia. It may be relevant that a large, uncontrolled study using high-dose multivitamin treatment (including vitamin E) together with long-term neuroleptic administration (27) reported a remarkably low incidence of tardive dyskinesia. Additional well-controlled studies are needed to clarify the possible efficacy of vitamin E in preventing tardive dyskinesia.

The therapeutic efficacy of vitamin E, although minor, supports the free-radical hypothesis of tardive dyskinesia. Vitamin E is a potent free-radical scavenger, and symptom improvement may be due to a reduced concentration of free radicals. This implies that free radicals are relevant to the pathogenesis of tardive dyskinesia. Alternatively, vitamin E could work in other ways. For example, it could alter neurotransmission in neurons related to movement, such as dopaminergic or $\gamma$-aminobutyric acid-ergic neurons. Although there are no data to support such highly speculative possibilities, they are alternatives to the antioxidant hypothesis. One potential problem with an antioxidant mechanism of action arises when trying to explain how a reduction in free radicals could improve symptoms caused by preexisting neuronal injury. This, however, is not an unreasonable hypothesis because other basal ganglia disorders can improve after neurotoxic agents are removed. In Wilson's disease, for example, chelation of excess copper both prevents progression and often improves preexisting abnormal movements (28).

In conclusion, the data suggest that vitamin E treatment has a mild beneficial effect in patients who have had tardive dyskinesia for a brief time. Vitamin E's effect did not appear to be due to an increase in serum neuroleptic levels. Although larger replication studies are needed, vitamin E is relatively safe and may be a reasonable treatment alternative in patients with early tardive dyskinesia. Finally, although other possibilities need to be examined, these results offer some support for the free-radical hypothesis of tardive dyskinesia.

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# A Crossover Study of Focused Cognitive Therapy for Panic Disorder

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*Objective: This study sought to determine the short- and long-term effects of focused cognitive therapy for panic disorder. Method: Thirty-three psychiatric outpatients with the* DSM-III *diagnosis of panic disorder were randomly assigned to either 12 weeks of individual, focused cognitive therapy or 8 weeks of brief supportive psychotherapy based on principles of client-centered therapy. The patients who received supportive psychotherapy were subsequently given the opportunity to cross over to cognitive therapy for 12 weeks. Patients were rated for panic and depression before therapy, after 4 and 8 weeks of therapy, and at 6-month and 1-year follow-up. Results: Clinician ratings and self-ratings of panic frequency and intensity indicated that the focused cognitive therapy group achieved significantly greater reductions in panic symptoms and general anxiety after 8 weeks of treatment than did the group that received brief supportive psychotherapy. At 8 weeks, 71% of the cognitive therapy group were panic free, compared to 25% of the psychotherapy group. Moreover, 94% of the psychotherapy patients elected to cross over to 12 weeks of cognitive therapy. At 1-year follow-up, 87% of the group that received cognitive therapy only and 79% of the group that crossed over into cognitive therapy remained free of panic attacks. Conclusions: Focused cognitive therapy offers a promising nonpharmacological alternative for the treatment of panic disorder.*

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While the immediate effectiveness of benzodiazepines and imipramine in alleviating panic symptoms has been documented, certain problems, such as patients' resistance to medication, intolerance of side effects, withdrawal symptoms, and high relapse rates (71% to 95%) have also been reported (1–6). Consequently, alternative nonpharmacological approaches are worth exploring.

Behavioral interventions have been somewhat effective in the treatment of panic disorder (7–9). In the past few years, a cognitive approach that focuses on the patient's misinterpretation of bodily sensations or psychological experience as catastrophic has been advanced (10, 11). Treatment is designed to demonstrate to patients how they have misconstrued the "dangerousness" of their symptoms. Two controlled studies (8, 9) have indicated the efficacy of behavioral treatment with cognitive components. In addition, controlled outcome studies have supported the effectiveness of focused cognitive therapy aimed at modifying patients' attributions of the cause of panic-related bodily sensations (12, 13, and unpublished 1991 paper by D.M. Clark).

In a prospective trial, Sokol et al. (13) found that focused cognitive therapy was highly effective in reducing the frequency of panic attacks (from a pretreatment mean of 4.5 panic attacks per week to a posttreatment mean of no attacks per week). These results were maintained over a 1-year follow-up period.

The current study was a replication and extension of the study by Sokol et al. (13) with the addition of 8 weeks of brief supportive psychotherapy as a comparison treatment. This comparative therapy condition, based on Rogers's nondirective therapy (14), was selected to take into account the possibility of spontaneous recovery as well as improvements resulting from contact with a therapist and self-monitoring of panic symptoms. The study contained four components: 1) 8 weeks of focused cognitive therapy compared with 8 weeks of supportive therapy, 2) an additional 4 weeks of cognitive therapy for the experimental group, 3) cross-

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over of the patients who received supportive therapy to 12 weeks of cognitive therapy, and 4) 6-month and 1-year posttreatment follow-up for both groups.

## METHOD

Thirty-three subjects between the ages of 18 and 65 years were drawn from outpatients successively entered into therapy at our center. Diagnostic assessment was carried out by trained psychologists using the Structured Clinical Interview for DSM-III (SCID) (15). Patients who met the *DSM-III* criteria for panic disorder (N=27) or agoraphobia with panic attacks (N=6) were invited to participate in the study. Twenty-two patients had secondary axis I diagnoses of major depression or dysthymia, 11 had diagnoses of generalized anxiety, and one had a diagnosis of simple phobia. Nine patients (four who received cognitive therapy only and five who received brief supportive psychotherapy) had axis II diagnoses.

The majority of the patients had longstanding histories of panic disorder (for the whole group, mean=7.2 years, SD=6.8; for the cognitive therapy group, mean=6.2 years, SD=6.1; for the brief psychotherapy group, mean=8.4 years, SD=8.7). Twenty-nine of the 33 patients reported previous psychotherapeutic treatment for panic (mean number of years of previous treatment=2.4, SD=3.6). The mean number of panic attacks in the 3 weeks before entry into the study was 6.2 (SD=6.1) for the cognitive therapy patients and 8.4 (SD=8.7) for the brief psychotherapy patients. There were no significant differences between the group that received cognitive therapy only and the group that received brief supportive psychotherapy on any of these demographic and diagnostic variables. Furthermore, 16 (48%) of the patients were currently on a daily regimen of benzodiazepines and still met the *DSM-III* criteria for panic disorder; an additional subject was taking antidepressant medication.

Random assignment resulted in 17 subjects for focused cognitive therapy and 16 subjects for brief supportive psychotherapy. The cognitive therapy condition involved 12 weekly individual sessions with a trained cognitive therapist; the brief supportive psychotherapy condition involved 8 weeks of supportive contact with a trained therapist. Upon completion of 8 weeks of cognitive therapy or brief supportive psychotherapy, patients were given the option of an additional 12 weeks of therapy in the other condition.

Data on panic frequency and intensity and depression were obtained from the subjects' self-reports and the ratings of independent clinicians before treatment and at 6- and 12-month follow-up. In addition, subjects assigned to the cognitive therapy group were evaluated after 4, 8, and 12 weeks of therapy, while the brief supportive psychotherapy subjects were assessed after 4 and 8 weeks. The brief supportive psychotherapy subjects who crossed over into cognitive therapy at the end of 8 weeks (crossover group) were reassessed after 12 weeks of cognitive therapy.

All 17 subjects in the cognitive therapy group completed the full 12 weeks of cognitive therapy, with four patients requiring up to four sessions beyond the 12-week protocol. In addition, 6-month and 1-year follow-up data were available on 15 of the cognitive therapy group. In the brief supportive psychotherapy condition, the 16 patients completed the 8 weeks of supportive therapy, and all chose to cross over into cognitive therapy. However, one patient subsequently completed only two sessions of cognitive therapy and then dropped out of treatment. Follow-up data were available on 14 of the crossover subjects.

Therapists followed a detailed treatment manual for the focused cognitive therapy of panic (16). The treatment is a form of brief, structured psychotherapy based on the hypothesis that panic attacks are the result of a vicious cycle involving fear of imminent physical or psychological disaster (17) arising from the misinterpretation of certain bodily sensations or psychological experiences (10, 11). For example, when heart palpitations or chest pains are misinterpreted as signs of an impending heart attack, this will lead to an escalation of the patient's symptoms of anxiety and panic. Cognitive strategies are designed to break the vicious cycle of panic by providing corrective information and experiences that result in the reattribution of unpleasant physiological or affective phenomena to nonpathological and less threatening sources.

Qualified postdoctoral therapists met weekly for 30-minute sessions with the patients who received brief supportive psychotherapy. Since the patients were requested to self-monitor their panic symptoms, a review of their weekly panic logs was the initial focus of the weekly sessions. The therapists applied Rogers's basic principles of unconditional positive regard, genuineness, and accurate empathy in order to establish a supportive, trusting therapeutic relationship with the patients. The therapists' technique was largely nondirective and included active listening, reflecting, and paraphrasing (14). On occasion, nonpanic issues were addressed if they became pressing. However, by taking a nondirective approach, the therapists did not apply specific interventions focused on alleviating panic symptoms.

At each assessment interval, independent clinical raters reviewed patients' daily logs of panic frequency to determine whether the recorded panic attacks actually met the *DSM-III* criteria for panic. In addition, self-ratings of weekly panic frequency and intensity (on a scale of 1–5) were obtained from subjects' responses on the Mobility Inventory for Agoraphobia (18).

Psychometric data were also collected on each testing occasion. The Beck Depression Inventory (19) and the Beck Anxiety Inventory (20) were administered to assess the intensity of depressive and general anxiety symptoms. A 60-item Specific Fear Inventory (unpublished 1985 paper by A.T. Beck and G. Brown) was given to assess individuals' level of situational distress and avoidance. The upset and avoidance scores of the 13-item Fear of Travel subscale were used for the analy-

**TABLE 1. Clinical Features of Patients With Panic Disorder Before Treatment and After 4 and 8 Weeks of Cognitive Therapy or Brief Supportive Psychotherapy[a]**

| | Before Treatment[b] | | After 4 Weeks of Treatment | | After 8 Weeks of Treatment | |
|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | Mean | SD |
| Panic attacks per week | | | | | | |
| Clinician rating | | | | | | |
| Cognitive therapy group | 5.6 | 4.0 | 1.4 | 1.9 | 0.4 | 0.6 |
| Psychotherapy group | 4.4 | 4.6 | 3.2 | 4.3 | 3.1 | 4.1 |
| Self-rating | | | | | | |
| Cognitive therapy group | 5.2 | 4.2 | 2.0 | 3.6 | 0.8 | 1.3 |
| Psychotherapy group | 5.5 | 5.5 | 3.7 | 4.6 | 3.5 | 4.1 |
| Self-rating of panic intensity (scale of 1–5) | | | | | | |
| Cognitive therapy group | 3.3 | 1.1 | 1.9 | 1.5 | 1.2 | 1.8 |
| Psychotherapy group | 3.0 | 1.1 | 2.8 | 1.4 | 2.5 | 1.5 |
| Beck Anxiety Inventory score | | | | | | |
| Cognitive therapy group | 30.2 | 10.3 | 19.1 | 12.1 | 14.8 | 13.2 |
| Psychotherapy group | 31.4 | 9.5 | 27.3 | 12.8 | 26.7 | 13.8 |
| Beck Depression Inventory score | | | | | | |
| Cognitive therapy group | 15.9 | 6.5 | 9.3 | 5.4 | 6.8 | 5.9 |
| Psychotherapy group | 18.8 | 7.6 | 15.3 | 9.8 | 13.7 | 11.1 |
| Specific Fear Inventory | | | | | | |
| Upset score | | | | | | |
| Cognitive therapy group | 24.1 | 9.1 | 18.1 | 8.1 | 14.9 | 7.5 |
| Psychotherapy group | 23.4 | 13.7 | 19.6 | 13.5 | 19.5 | 15.1 |
| Avoidance score | | | | | | |
| Cognitive therapy group | 16.9 | 7.8 | 15.3 | 7.7 | 11.7 | 6.2 |
| Psychotherapy group | 18.8 | 12.4 | 15.3 | 11.7 | 14.9 | 12.5 |

[a] Because of missing values for some variables, Ns varied across analyses from 14 to 17 patients in the cognitive therapy group and 15 to 16 patients in the brief supportive psychotherapy group.

[b] Data are based on the intake evaluation.

ses, since a previous study suggested that this subscale showed the best discrimination of panic disorder.

Two-by-three repeated measures multiple analyses of variance (MANOVAs) with group (cognitive therapy only versus brief supportive psychotherapy) as the between-group factor and time (pretreatment, 4 weeks, and 8 weeks) as the within-subjects factor assessed treatment effectiveness over the first 8-week period. Separate MANOVAs were conducted on clinician-rated panic frequency and Beck Depression Inventory and Beck Anxiety Inventory scores. Self-rated panic frequency and severity were analyzed in the same MANOVA, as were the Specific Fear Inventory upset and avoidance scores. Significant multivariate F values were followed up with univariate F tests and polynomial trend analysis on the repeated measure. A second series of MANOVAs analyzed data collected over the pretreatment, posttreatment, and 6- and 12-month follow-up periods for the cognitive therapy group and the 16 brief supportive psychotherapy patients who crossed over into cognitive therapy. Violation of the assumption of normality necessitated that logarithmic transformations be performed on the self- and clinician ratings of panic.

Significant quadratic and cubic trends frequently emerged with trend analysis on the main effect for time or the Time by Group interaction. This suggests some fluctuation in subjects' scoring across the different assessment intervals. Since the main hypotheses of the study were tested with the linear component, only this is reported here. An extended report of the study, including the complete trend analysis, is available from the first author on request.

## RESULTS

Analysis with t tests revealed that before treatment, there were no significant differences between the cognitive therapy patients and the brief supportive psychotherapy patients on any of the measures of panic symptoms, depression, general anxiety, and situational fear and avoidance. Since there were no significant pretreatment between-group differences on these dependent variables, it was not necessary to covary out pretreatment levels in the MANOVAs we report.

### *Cognitive Therapy Versus Brief Supportive Therapy at 8 Weeks*

Table 1 presents data on the dependent measures for the cognitive therapy and brief supportive psychotherapy groups during the pretreatment period and after 4 and 8 weeks of treatment. Analysis of independent clinician ratings of panic frequency revealed a significant Group by Time interaction ($F=6.54$, $df=2, 27$, $p<0.005$) with a significant linear component ($F=12.94$, $df=1, 28$, $p<0.001$). Similarly, analysis of self-rated panic frequency and intensity produced a significant Group by Time interaction ($F=2.70$, $df=4, 27$, $p<0.05$) with significant linear components on both frequency ($F=7.15$, $df=1, 30$, $p<0.01$) and intensity ($F=10.63$, $df=1, 30$, $p<$

0.01). These results indicate that the cognitive therapy subjects obtained significantly greater reductions in clinician-rated and self-rated panic frequency than did the subjects who received brief supportive psychotherapy.

A Group by Time interaction ($F=3.32$, $df=2, 58$, $p<0.05$) with a significant linear trend ($F=5.25$, $df=1, 29$, $p<0.03$) emerged for the Beck Anxiety Inventory scores but not for the Beck Depression Inventory scores. (The Mauchley test of sphericity indicated a violation of the homogeneity of covariance assumption with all of our analyses except those for the anxiety inventory scores. As a result we used the more conservative multivariate approach except in the case of the anxiety scores, in which it was possible to use a repeated measures analysis of variance with a Greenhouse-Geisser correction to the degrees of freedom.) However, the linear component ($F=5.25$, $df=1, 29$, $p<0.03$) for the main effect for time ($F=11.04$, $df=2, 29$, $p<0.0001$) was significant for the Beck depression scores.

These results indicate that although the cognitive therapy patients evidenced significantly greater reductions in general anxiety than the brief supportive psychotherapy patients, both groups experienced a significant decline in depression scores over the first 8 weeks of treatment. Finally, analysis of the upset and avoidance scores on the Fear of Travel subscale of the Specific Fear Inventory revealed a Group by Time interaction ($F=2.87$, $df=4, 27$, $p<0.04$) with a significant linear component for the upset score only ($F=7.51$, $df=1, 30$, $p<0.01$). This indicates that the cognitive therapy group had significantly lower upset scores on the Specific Fear Inventory at 8 weeks than did the brief supportive psychotherapy group. However, no significant between-group differences in the avoidance scores emerged.

In summary, the repeated measures MANOVA produced three F statistics, one for the interaction and two main effects for time and group. The interaction term tests whether the downward trends over treatment sessions are parallel. The partitioning of the interactions into linear components indicated that on all of our dependent measures except the Beck Depression Inventory score and the Specific Fear Inventory avoidance score, the cognitive therapy group had a stronger downward trend in symptoms than the brief supportive psychotherapy group.

Chi-square analysis comparing presence versus absence of weekly panic attacks revealed that on the basis of clinician ratings, a significantly larger number of the cognitive therapy patients than of the brief supportive psychotherapy patients had no panic attacks at 8 weeks (cognitive therapy group, N=12, 71%; brief psychotherapy group, N=4, 25%). This difference in outcome was significant for the clinicians' ratings of panic frequency ($\chi^2=5.20$, $df=1$, $p<0.02$) and the patients' self-reports ($\chi^2=5.37$, $df=1$, $p<0.02$).

### *Posttreatment and Follow-Up*

Table 2 presents data on the dependent variables for the cognitive therapy and crossover groups before treatment, after treatment, and at 6-month and 1-year follow-up.

Analysis of end-state functioning indicated that after 12 weeks of focused cognitive therapy, 16 (94%) of the 17 patients who received cognitive therapy only were free of weekly panic attacks according to the independent clinician ratings. The one patient showing only partial recovery transferred into another treatment program. For the crossover group, 10 (63%) of the patients were panic free at the end of treatment. Of the remaining crossover patients, three showed poor response to treatment, two evidenced partial recovery, and one failed to complete the treatment program. Three of these patients sought additional treatment for their panic symptoms.

A 2×4 MANOVA revealed a significant linear trend ($F=10.77$, $df=1, 17$, $p<0.001$) for the main effect of time ($F=9.42$, $df=3, 15$, $p<0.001$) on the independent clinician ratings of panic frequency. Analysis of self-rated panic frequency and intensity revealed a significant main effect for time ($F=26.74$, $df=6, 16$, $p<0.0001$) with linear trends for panic frequency ($F=9.07$, $df=1, 21$, $p<0.01$) and intensity ($F=10.52$, $df=1, 21$, $p<0.01$). These results indicate that both the cognitive therapy group and the crossover group maintained treatment gains at 1-year follow-up, with significantly fewer panic attacks at posttreatment assessment and follow-up than at pretreatment assessment. Moreover, analysis of end-state functioning indicated that at 1-year follow-up, 87% (N=13) of the cognitive therapy subjects and 79% (N=11) of the brief supportive psychotherapy subjects who crossed over into cognitive therapy were panic free.

MANOVA results on the Beck Depression Inventory and Beck Anxiety Inventory scores over the follow-up period revealed a main effect for time (for depression score, $F=5.39$, $df=3, 16$, $p<0.01$; for anxiety score, $F=13.57$, $df=3, 14$, $p<0.0001$) with a significant linear trend (depression score, $F=9.28$, $df=1, 18$, $p<0.01$; anxiety score, $F=22.98$, $df=1, 16$, $p<0.0001$). In addition, analysis of the Specific Fear Inventory upset and avoidance scores revealed a main effect for time ($F=4.69$, $df=6, 13$, $p<0.01$) with significant linear components for upset ($F=12.83$, $df=1, 18$, $p<0.01$) and avoidance ($F=7.65$, $df=1, 18$, $p<0.05$). Once again, these results indicate that the cognitive therapy and crossover subjects continued to have significantly lower Beck Depression Inventory, Beck Anxiety Inventory, and Specific Fear Inventory upset and avoidance scores at 1-year follow-up compared to their pretreatment levels. The failure to find a significant linear component on the Group by Time interaction indicates that cognitive therapy was equally effective in reducing panic and anxiety in the group that received cognitive therapy only and the crossover group.

## DISCUSSION

These findings represent a replication and extension of the naturalistic study by Sokol et al. (13). In contrast

**TABLE 2. Clinical Features of Patients With Panic Disorder Before Treatment, After Treatment With Cognitive Therapy Only or Crossover From Psychotherapy to Cognitive Therapy, and at 6-Month and 1-Year Follow-Up[a]**

| | Before Treatment[b] | | After Treatment[c] | | 6-Month Follow-Up | | 1-Year Follow-Up | |
|---|---|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Panic attacks per week | | | | | | | | |
| Clinician rating | | | | | | | | |
| Cognitive therapy group | 4.5 | 4.3 | 0.1 | 0.3 | 0.9 | 2.2 | 0.7 | 2.2 |
| Crossover group | 1.9 | 2.7 | 2.0[d] | 4.6 | 0.2 | 0.4 | 0.3 | 1.0 |
| Self-rating | | | | | | | | |
| Cognitive therapy group | 4.5 | 4.4 | 0.0 | 0.0 | 1.1 | 2.3 | 0.6 | 1.4 |
| Crossover group | 2.4 | 2.6 | 0.4 | 0.8 | 0.4 | 0.8 | 0.5 | 0.9 |
| Self-rating of panic intensity (scale of 1–5) | | | | | | | | |
| Cognitive therapy group | 3.1 | 1.1 | 0.0 | 0.0 | 0.8 | 1.5 | 0.7 | 1.4 |
| Crossover group | 2.4 | 1.4 | 0.9 | 1.7 | 0.9 | 1.7 | 0.7 | 1.3 |
| Beck Anxiety Inventory score | | | | | | | | |
| Cognitive therapy grouup | 28.1 | 10.8 | 9.8 | 12.2 | 9.1 | 6.6 | 8.4 | 7.8 |
| Crossover group | 27.7 | 9.9 | 14.7 | 11.3 | 9.7 | 7.9 | 11.1 | 10.6 |
| Beck Depression Inventory score | | | | | | | | |
| Cognitive therapy group | 14.2 | 6.8 | 6.6 | 6.7 | 6.4 | 7.5 | 6.7 | 8.4 |
| Crossover group | 11.7 | 8.9 | 7.1 | 8.7 | 4.0 | 5.4 | 6.9 | 7.7 |
| Specific Fear Inventory | | | | | | | | |
| Upset score | | | | | | | | |
| Cognitive therapy group | 24.9 | 9.3 | 14.4 | 7.0 | 14.9 | 9.3 | 13.4 | 10.8 |
| Crossover group | 21.5 | 16.9 | 19.4 | 14.4 | 13.4 | 13.5 | 13.5 | 12.9 |
| Avoidance score | | | | | | | | |
| Cognitive therapy group | 17.0 | 8.5 | 9.7 | 4.8 | 10.2 | 5.3 | 10.6 | 8.9 |
| Crossover group | 16.6 | 14.1 | 15.3 | 11.2 | 12.1 | 11.6 | 11.5 | 11.0 |

[a] Because of missing values for some variables, Ns varied across analyses from 9 to 12 patients in both groups.

[b] Data are based on the intake evaluation for the cognitive therapy group and the 8-week evaluation after brief supportive psychotherapy for the crossover group.

[c] The cognitive therapy group received 12 weeks of cognitive therapy only. The crossover group received 8 weeks of brief supportive psychotherapy followed by 12 weeks of cognitive therapy.

[d] This unexpectedly high posttreatment mean was due to an extreme outlier. That subject had 14 panic attacks after 12 weeks of cognitive therapy. However, the mean number of posttreatment panic attacks for the remaining 14 subjects was 0.9 (SD=1.6).

to that study, however, the present trial of cognitive therapy was compared with a trial of supportive psychotherapy for the first 8 weeks—the period during which the greatest therapeutic improvement has been shown to occur (13). The cognitive therapy patients improved significantly more on various symptom measures of panic and anxiety than did the comparison group.

By the end of the prescribed 12 weeks of treatment, patients receiving cognitive therapy showed a significant and clinically meaningful reduction in the number of panic attacks. A parallel improvement was evident on self-report measures of depression, anxiety, and situational avoidance. These therapeutic gains were stable up to 1-year follow-up for 13 of the 15 patients enrolled in the follow-up study. One patient showed a complete clinical relapse and another a partial recurrence of panic symptoms.

Fifteen of the 16 patients who crossed over from supportive therapy to cognitive therapy also showed a significant reduction in panic attacks, avoidance, and symptoms of depression and anxiety at the end of treatment. Of the 14 crossover patients on whom follow-up data were available, 11 (79%) were free of panic attacks by 1 year; one patient continued to show only partial improvement, one had a complete clinical relapse, and one had a partial recurrence of panic symptoms.

Sixteen of the subjects who entered the study were regularly taking some form of medication. In fact, all but one of these patients were taking daily doses of a benzodiazepine but continued to meet the *DSM-III-R* criteria for panic disorder. At the end of treatment and at 1-year follow-up, only four (25%) of the 16 medicated patients had completely discontinued their medication, although a further seven (44%) of these patients had reduced their medication levels. Because of the limited sample size, it was not possible to investigate systematically the influence of continued use of medication on the effectiveness of cognitive therapy. We are currently in the process of addressing this question with a larger sample of panic patients.

The drop in depression scores in the brief supportive psychotherapy group may be attributed to the fact that patients in that group viewed their therapists as warm and understanding. Although the therapists may have had doubts about the efficacy of the supportive therapy in relieving panic symptoms, they did make a strong effort to apply the principles of nondirective therapy (14). The fact that depression but not panic or anxiety declined during the 8 weeks of supportive therapy suggests that the therapists' emphasis on the therapeutic relationship had an impact on depression even though panic attacks were not relieved.

In conclusion, this study adds to the growing number of controlled and open trials indicating that panic attacks are particularly sensitive to cognitive or cognitive-behavioral interventions. These cumulative findings provide support for the efficacy of cognitive therapy for panic attacks. In addition, the relatively low rates of relapse and recurrence and the absence of side effects point to special advantages of this form of psychosocial treatment.

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# Qualitative Assessment of Brain Morphology in Acute and Chronic Schizophrenia

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Objective: *Neuroimaging studies of brain morphology in schizophrenia have used predominantly morphometric techniques to assess brain scans. However, as currently implemented, such methods are not particularly helpful in the routine assessment of individual patients. The purpose of this study was to evaluate brain morphology seen with magnetic resonance imaging (MRI) by qualitative assessment, the most frequently used method in clinical practice for evaluating brain scans.* Method: *First-episode (N=62) and chronic, multiepisode (N=24) schizophrenic patients and healthy comparison subjects (N=42) underwent MRI of the whole head in a sequence that provided 63 contiguous brain slice images. Each subject received a rating of normal, questionably abnormal, or definitely abnormal for four brain regions (lateral ventricles, third ventricle, medial temporal lobe structures, and frontal/parietal cortex) and a global rating.* Results: *The schizophrenic patients had significantly higher global rates of abnormal morphology (first-episode group, 31%; chronic group, 42%) than the normal subjects (5%). The highest regional rates of abnormalities were seen in the lateral ventricles and the lowest in the frontal/parietal cortex. Although the chronic patients had generally higher abnormal rates than the first-episode patients, these differences were not statistically significant. The qualitative ratings of brain morphology were significantly correlated with quantitative assessments performed in separate studies.* Conclusions: *Despite its limits in sensitivity (and until quantitative morphometric techniques are made practical and more widely available), qualitative evaluation of MRI scans can be a useful technique in research and clinical evaluation of patients with schizophrenia.*

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Post-mortem and in vivo imaging studies of the brain have demonstrated morphologic abnormalities in patients with schizophrenia (1–3). These alterations include enlargement of the lateral and third ventricles, enlargement of the cortical sulci of the frontal, temporal, and parietal regions, and reduction in the volume of the medial temporal lobe structures (2–11). Despite the consistency of these findings, it is apparent that the pathology in schizophrenia is relatively subtle in magnitude compared to that of other neurodegenerative disorders such as Alzheimer's disease and Huntington's disease. Generally speaking, standard neuroradiologic evaluations based on visual inspection regard as abnormal only the extreme examples of the pathomorphology characteristic of schizophrenia. Recent research on brain morphology in schizophrenia has emphasized morphometric statistical studies of post-mortem brains, computed tomography (CT), and magnetic resonance imaging (MRI) (1–11).

MRI has shown a clear advantage over CT by virtue of its multiplanar capability, high tissue contrast and resolution, and absence of ionizing radiation. Medial temporal lobe structures can be well visualized, especially in coronal MRI slices. Several MRI studies of schizophrenic subjects have reported increased ventricle size, altered midline dimensions in the corpus callosum, and reduced frontal and temporal lobe size (4–15). All of these studies, however, used morphometric meth-

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ods and described statistical differences between patients and nonpsychiatric control subjects. While they are necessary to establish scientific evidence of group differences, morphometric methods are not very helpful in the routine clinical assessment of an individual scan. One solution to this problem of what is normal or abnormal in an MRI scan of a single schizophrenic subject would be to collect well-defined normative quantitative data for different age groups and to compare individual patients' values with the appropriate age- and sex-defined range of normal anatomic volumes. To date, this principle, which is widely used in all fields of clinical medicine, has not been applied in MRI assessment of the brain, since standardized age- and sex-related morphometric data (e.g., for volumes of ventricular, cortical, and subcortical structures) are not yet available and since standardized mensuration systems are not yet widely used.

For the time being, qualitative assessment remains the most frequently applied method in clinical medicine to determine whether a scan is normal or not (16). Taking this fact into account, this article addresses the following questions. 1) Can brain abnormalities be seen in MRI scans of patients when qualitative assessment, as it is usually performed in clinical practice by psychiatrists or neuroradiologists, is used? 2) How frequently do these abnormalities occur in different brain regions of schizophrenic subjects as compared to normal subjects? 3) How strong is the correlation between qualitative assessment and quantitative measurement of various brain structures?

To investigate these questions, we evaluated brain morphology by using blind qualitative examination of MRI scans of the brain in three groups of subjects: first-episode schizophrenic patients with little or no prior neuroleptic treatment, treatment-refractory chronic schizophrenic patients, and normal volunteers.

## METHOD

Schizophrenic subjects were selected from patients in two research protocols that were being conducted at a hospital. The first was a prospective study of psychobiology in schizophrenia, which ascertained patients who had entered the hospital in their first episode of schizophrenia and had not had previous neuroleptic treatment (this study has been described in detail elsewhere [17]). Diagnoses were determined according to the Research Diagnostic Criteria (RDC) (18) on the basis of information from a structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia (19), and confirmed by long-term follow-up (1–3 years). The second protocol was a study of clozapine treatment in refractory schizophrenia (20). Patients ascertained for this study were diagnosed by a research psychiatrist as having chronic schizophrenia (according to *DSM-III-R*) on the basis of a comprehensive clinical evaluation and a history of resistance to treatment. This was defined as the persistence of psychotic symptoms at a significant level of severity despite adequate independent trials (6 weeks at 1000 mg/day in chlorpromazine equivalents) of three neuroleptics from two different biochemical classes.

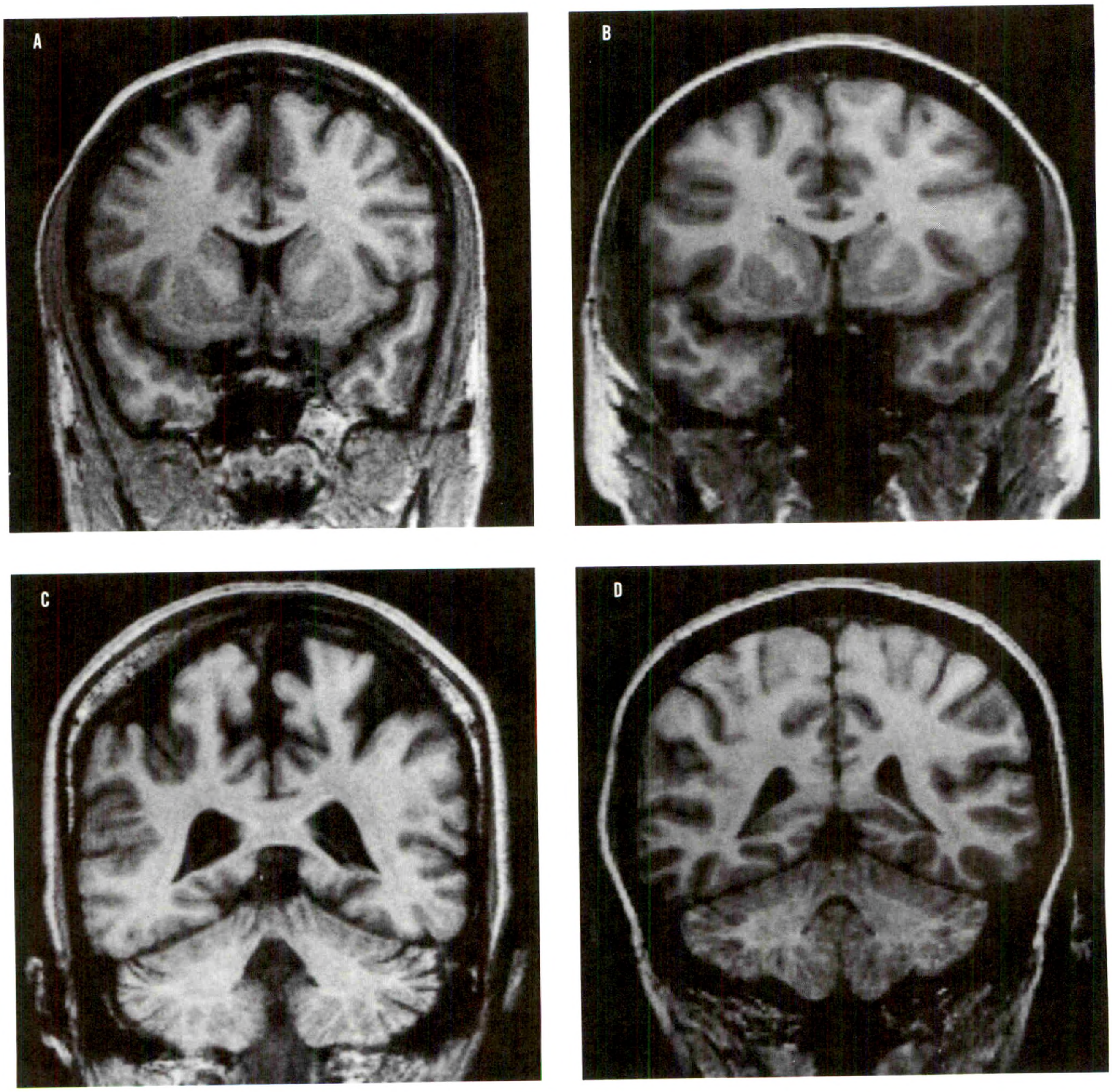
Normal comparison subjects were recruited from the medical center staff and community through advertisements. The volunteers were screened for medical and psychiatric illness and history of substance abuse (unpublished paper of J.A. Walsleben et al.).

None of the patients or comparison subjects had a history of substance dependence or current abuse or a history of chronic neuromedical illness or drug treatment known to affect the brain (e.g., corticosteroids). The normal comparison subjects were selected with regard to matching the demographic characteristics of the patient groups.

The subjects were scanned in a 1.0-tesla whole-body MRI system (Siemens Magnetom) with a dedicated head coil. Brain images were obtained in the coronal plane through the whole head in 3.1-mm contiguous slices by using a 50° FLASH sequence with a repetition time (TR) of 40 msec and an echo time (TE) of 15 msec in one acquisition. This sequence provided 63 contiguous slices in a 256×256-pixel matrix with no zoom factor and a resolution of 1.0×1.0×3.1 mm in 11 minutes (this procedure has been fully described by Ashtari et al. [21]).

For analysis, the imaging data were transferred by means of magnetic tape onto a SUN work station for quantitative assessment (the results of which are described in references 6 and 22 and an unpublished paper by B. Bogerts et al.). Video film hard copies were printed for visual qualitative evaluation. MRI scans of patients and comparison subjects were combined in a randomized order and evaluated independently, under blind conditions, by two research psychiatrists (B.B. and G.D.) trained in neuroanatomy and radiologic assessment. On the coronal spin-lattice relaxation time ($T_1$)-weighted scans, four regions were assessed: lateral ventricles, third ventricle, frontal and parietal cortex, and medial temporal structures. Qualitative evaluations were made on a 3-point scale (normal, questionable, abnormal). The criteria that were developed to classify regions of interest on this scale are described in appendix 1. Their essence can be summarized as follows. An abnormal cortex was defined on the basis of the prominence of the interhemispheric fissure, cortical sulci, and the cortical subarachnoid space in the frontal and/or parietal regions (figure 1, A–D). Abnormality of the lateral ventricles was determined on the basis of increased size of the body or frontal or occipital horns and/or blunting of the lateral angles (figure 2, A–D, and figure 3, A–C). Abnormality of the third ventricle was determined on the basis of its width (figure 3, C–E). Evaluation of the medial temporal structures was based on the size and shape of the hippocampal formation and the size of the temporal horn throughout its anteroposterior extension (shown at the level of the mammillary body in figure 3, E–G). An abnormal rating for the medial temporal structures was given if there was a

**FIGURE 1.** Coronal Magnetic Resonance Images of a 20-Year-Old Man (A and C) and a 30-Year-Old Woman (B and D) at Two Different Levels[a]

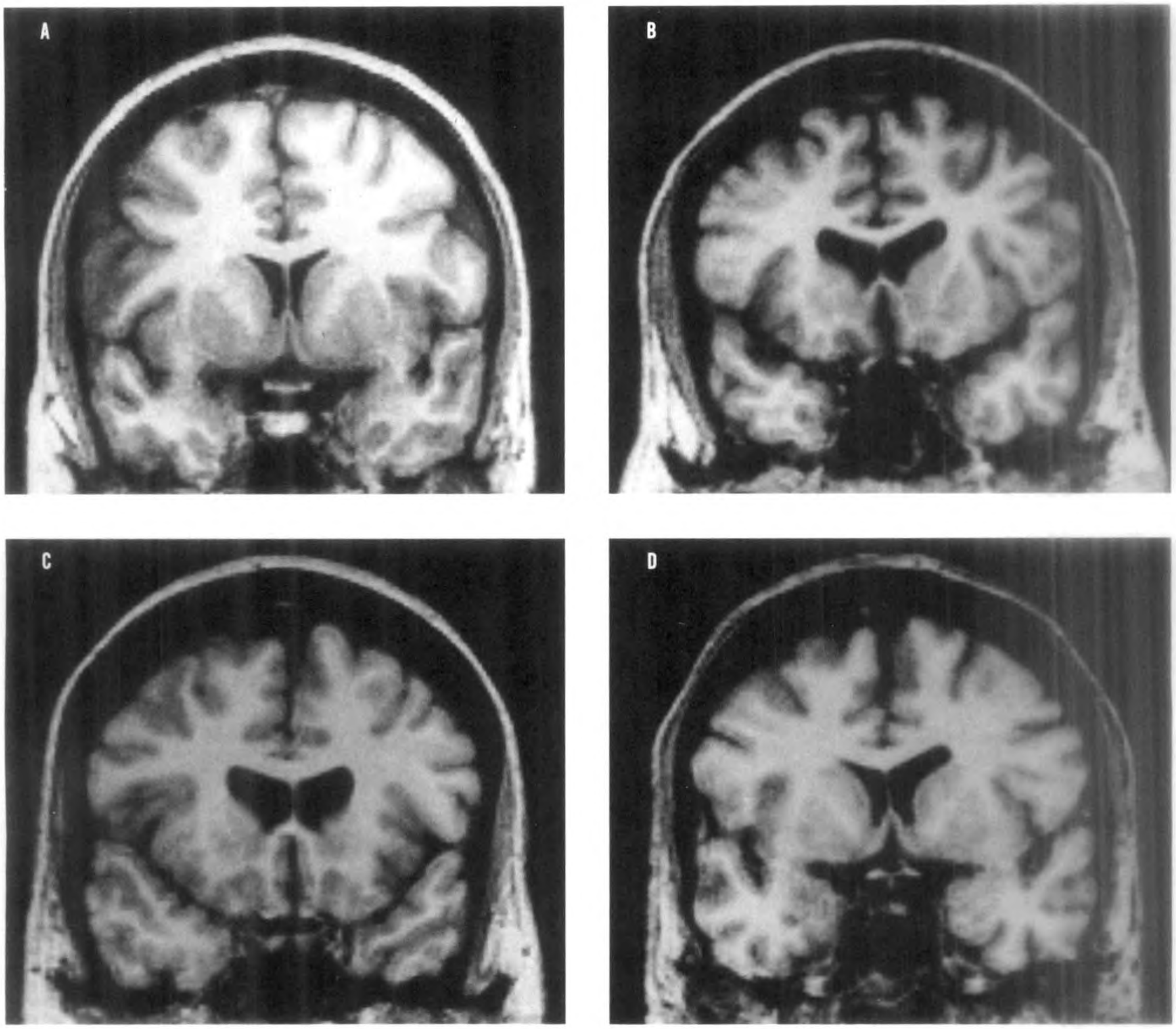


[a] A and B show the frontal cortex just posterior to the genu of the corpus callosum. C and D show the parietal cortex at the splenium of the corpus callosum. A illustrates reduced frontal cortical volume and increased interhemispheric fissure, while B shows normal anatomy at the same level. C illustrates markedly reduced parietal cortical volume and increased subarachnoid space and interhemispheric fissure, while D shows normal anatomy at the same level.

clear reduction in the size or a dysplastic configuration of the hippocampal formation or an increase of the temporal horn size on the right and/or left side of the brain (figure 3, A–G). A subject was classified as having a global abnormality if he or she had a definite abnormal rating in one or more of the four brain regions.

The interrater reliability of the two research psychiatrists was determined by computing the intraclass correlations (kappas) (23) of their ratings. The kappas for the four brain regions (frontal and/or parietal cortex, lateral ventricles, third ventricle, and medial temporal structures) were 0.72, 0.77, 0.77, and 0.60, respectively. Complete agreement was reached on 75% of the ratings in each of the four regions. For only one region (medial temporal structures) and on only one qualitative rating was there disagreement by a factor of 2 (one psychiatrist gave a rating of 0 [normal] and the other, 2 [abnormal]). In approximately 25% of the ratings, the raters disagreed by

FIGURE 2. Coronal Magnetic Resonance Images Showing Normal and Enlarged Lateral Ventricles[a]

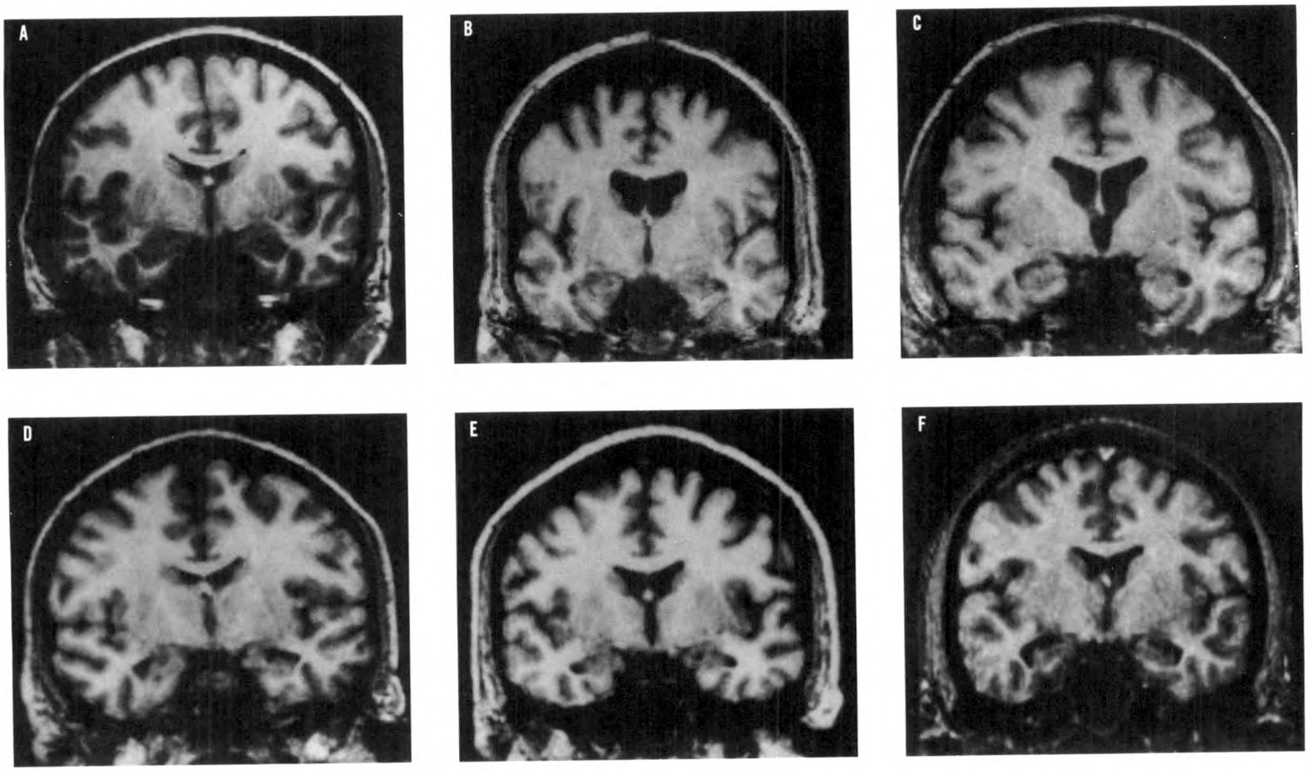


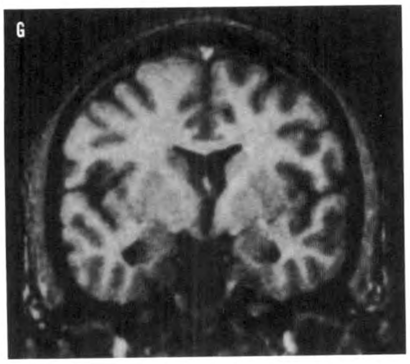
[a] A: Image of a 30-year-old woman at the level of the optic chiasm. The configuration of the lateral ventricles is normal.
B and C: Images of a 25-year-old man and a 36-year-old woman at levels of one and three slices posterior to the genu of the corpus callosum, respectively, showing lateral ventricle enlargement. Note the blunted lateral angle of the ventricles, which can commonly be seen in elderly normal subjects but is rare in younger normal subjects.
D: Image of a 25-year-old man at the level of the optic chiasm, with enlargement of the left frontal horn (the patient's left is on the right in the figure). This asymmetric enlargement is distinct from A, B, and C, which show bilateral involvement of the ventricles.

1 point (either 0 [normal] versus 1 [questionable] or 1 [questionable] versus 2 [abnormal]).

In contrast to morphometric procedures, qualitative assessment of brain structures in CT and MRI depends largely on the observers' experience and orientation and the clinical (or scientific) context in which they view the scan. Relevant factors (e.g., ventricle size is age related, and what might be normal for age 60 may not necessarily be normal for age 20) are frequently overlooked. To establish the validity of the qualitative ratings, they were compared with the volumes of all components of the lateral and third ventricles and the medial temporal structures (amygdala-hippocampus complex) that had been previously determined with a computerized mensuration system (6, 21–24). The qualitative ratings (normal, questionable, abnormal) of the lateral ventricles, third ventricle, and medial temporal structures and the quantitatively determined volumes of the same structures were compared by analysis of variance (ANOVA) and found to be significantly associated in the ANOVAs that had the quantitative measure as the dependent measure and the qualitative rating as the between-groups factor (for the right and left lateral ventricles, respectively, $F=16.6$, $df=2, 31$, $p<0.0001$, and $F=27.9$, $df=2, 31$, $p<0.0001$; for the third ventricle, $F=17.2$, $df=2, 31$, $p<0.0001$; and for the

**FIGURE 3. Coronal Magnetic Resonance Images at the Level of the Mammillary Body and the Level of Monro's Foramen**[a]





[a] A: Image of a 21-year-old man at the level of the mammillary body, showing normal anatomy of the lateral and third ventricles, the anterior hippocampus, and the temporal horn.
B: Image of a 21-year-old man at the level of the mammillary body, with lateral ventricle enlargement and normal-appearing third ventricle and medial temporal structures.
C: Image of a 21-year-old man at the level of the mammillary body, with marked enlargement of the third ventricle, moderate enlargement of the lateral ventricles, questionable enlargement of the temporal horns, and normal-appearing medial temporal structures.
D and E: Images of a 16-year-old girl and a 22-year-old woman at the level of the mammillary body, showing bilateral reduction in hippocampal volumes. D also shows normal third and lateral ventricles, while E shows questionably enlarged third and lateral ventricles.
F and G: Images of a 21-year-old man. F, at the level of Monro's foramen, shows reduced amygdala volume, enlarged temporal horns bilaterally, and a questionably enlarged third ventricle and lateral ventricle. G, at the level of the mammillary body, shows reduced hippocampal volume, enlarged temporal horns bilaterally, and a questionably enlarged lateral ventricle.

right and left medial temporal structures, respectively, F=7.5, df=2, 28, p=0.003, and F=3.4, df=2, 28, p=0.05). The weaker association of the medial temporal structures is explained by the fact that this brain region was assessed as abnormal if the hippocampus looked dysplastic or if the temporal horn was enlarged (the two changes did not always coincide). Therefore, correlations of the qualitative ratings of the medial temporal structures with the volume of one or the other structure were necessarily smaller. In addition, the shape of the medial temporal structures is less homogeneous and more variable than that of the ventricles, making reliable assessment more difficult. Data on cortical volume were not available; hence, no analyses for the cortex were performed.

Categorical data analysis (chi-square test) was used to compare the three groups on the distribution of brain pathomorphology, as well as on the categorical demographic and clinical variables such as race and diagnosis. ANOVA was used to compare the groups on the number of affected regions, as well as on the continuous demographic and clinical variables such as age. Because three groups were being compared in these analyses, significant results were followed up to test which groups actually differed from each other. These comparisons were of special interest in the contrast between the first-episode and the chronic, treatment-refractory groups. These between-group comparisons were done with chi-square and t tests.

## RESULTS

The study groups consisted of 62 patients in their first episode of schizophrenia, 24 treatment-refractory patients with chronic schizophrenia, and 42 normal vol-

**TABLE 1. Characteristics of Subjects in a Study of Qualitative Assessment of Brain Morphology**

| | Schizophrenic Patients | | | | Normal Comparison Subjects (N=42) | |
|---|---|---|---|---|---|---|
| | First-Episode (N=62) | | Chronic (N=24) | | | |
| Characteristic | N | % | N | % | N | % |
| Male sex | 33 | 53[a] | 21 | 88 | 21 | 50[b] |
| Race/ethnicity | | | | | | |
| White | 27 | 44[c] | 22 | 92 | 30 | 70[d] |
| Black | 21 | 34 | 1 | 4 | 3 | 7 |
| Hispanic | 9 | 15 | 1 | 4 | 4 | 10 |
| Asian | 5 | 8 | 0 | 0 | 5 | 13 |
| Diagnosis | | | | | | |
| Schizophrenia | 49 | 79 | 22 | 92 | — | — |
| Schizoaffective disorder | 13 | 21 | 2 | 8 | — | — |

[a] Significantly different from the chronic group ($\chi^2$=7.3, df=1, p=0.001).
[b] Significantly different from the chronic group ($\chi^2$=8.7, df=1, p=0.003).
[c] Significantly different from the chronic group ($\chi^2$=16.5, df=3, p<0.001).
[d] Significantly different from the first-episode group ($\chi^2$=10.1, df=3, p=0.02).

unteers. As would be expected, the first-episode patients were younger (mean age=24.1 years, SD=5.8) than the chronic schizophrenic patients (mean=29.1 years, SD=5.7) and the comparison subjects (mean=28.8 years, SD=7.5) (F=8.9, df=2, 125, p=0.001). The sex ratio, racial/ethnic composition, and diagnoses of the three groups are shown in table 1. There was a higher proportion of male patients in the chronic schizophrenic group than in the first-episode and normal groups. There was also variation in the racial/ethnic distribution of the groups, with the chronic schizophrenia group having the highest proportion of white subjects. The normal comparison subjects had a higher education level (1=graduate school, 2=college graduate, 3=some college, 4=high school graduate) than the patient groups (normal subjects, mean=2.0, SD=0.9; first-episode patients, mean=3.4, SD=1.1; chronic patients, mean=3.5, SD=0.9). The patient groups were predominantly schizophrenic; the balance had schizoaffective disorder. The chronic, multiepisode group obviously had a longer duration of illness (mean=478 weeks, SD=291) than the first-episode group (51 weeks, SD=85) (t for unequal variance=6.9, df=25, p<0.001).

The prevalence rates of brain pathomorphology by region are shown in table 2. The schizophrenic patients had higher abnormal rates (questionable and definite) than the comparison subjects in all four regions. With the global criterion of defining a patient as abnormal if at least one of the four brain regions assessed was abnormal (or questionable if at least one of the four brain regions assessed was questionable), 57% of the comparison group were rated normal, 33% of the first-episode patient group were rated normal, and 25% of the chronic patient group were rated normal ($\chi^2$=15.8, df=4, p=0.003). The highest prevalence of abnormal morphology in any specific region was in the lateral ventricles, where the normal rate was 29% for the chronic patients, 56% for the first-episode patients, and 79% for the normal subjects ($\chi^2$=18.2, df=4, p=0.001). On visual inspection, the most noticeable feature of lateral ventricle enlargement was the blunting of the lateral corner between the caudate nucleus and corpus callosum (figure 2, B and C). This was seen particularly in the left lateral ventricle, which in the quantitative and qualitative assessments was frequently preferentially affected (figure 2, D). (For additional information on the quantitative differences in left and right ventricle volume, see reference 22.) The lowest rates of pathomorphology were seen in the frontal/parietal cortical regions, where the rates of normalcy for the first-episode, chronic, and normal groups were 76%, 75%, and 93%, respectively ($\chi^2$=8.8, df=4, p=0.07). The low rates of pathomorphology in this region could be due to the fact that cortical sulci are less easily visualized in the coronal plane than in the axial plane. In addition, the substantial variability of size, shape, and configuration of cortical sulci and gyri make qualitative assessment of pathomorphology of this region more difficult than for simpler structures like the ventricles.

Although the chronic schizophrenic patients appeared to be more severely affected than the first-episode schizophrenic patients, comparisons between the first-episode and chronic groups revealed only one region, in the lateral ventricles, where marginally significant differences were exhibited ($\chi^2$=5.4, df=2, p=0.07).

Abnormal morphology ratings in all four regions for the entire study group were significantly intercorrelated (table 3). The highest correlations were between the lateral ventricles and the medial temporal structures, between the lateral ventricles and the third ventricle, and between the third ventricle and the medial temporal structures. The lowest correlations were between the frontal/parietal cortex and the other structures.

To examine the distribution of abnormal morphology in the study group in another way, we classified subjects by the number of regions that were rated as definitely abnormal (table 4). Comparisons of the three subject groups on the number of regions affected within each subject revealed that the chronic schizophrenic group was most severely affected, with a mean of 0.71 regions (SD=1.08) definitely abnormal, followed by the first-episode schizophrenic group, with a mean of 0.47 abnormalities (SD=0.78), and the normal group, with a mean of 0.05 abnormalities (SD=0.22). The three groups differed in the mean number of pathomorphologic regions when the abnormal rating was used as the criterion level (F=7.3, df=2, 125, p=0.001) and when the questionable rating was used as the criterion level (F=7.5, df=2, 125, p=0.0009). Although each of the patient groups differed significantly from the normal comparison group, they did not differ from each other by either the abnormal or the questionable criterion level (t=1.1, df=84, p=0.26, and t=1.2, df=84, p=0.25, respectively).

To examine the effect of gender, we compared the rates of brain pathomorphology for men and women in the combined patient group (N=86). The male patients

**TABLE 2. Pathomorphology Ratings by Brain Region in First-Episode and Chronic Schizophrenic Patients and Normal Comparison Subjects**

| Brain Region/ Physicians' Rating | Schizophrenic Patients: First-Episode (N=62) (A) N | % | Schizophrenic Patients: Chronic (N=24) (B) N | % | Normal Comparison Subjects (N=42) (C) N | % | Significant Differences (chi-square analyses) |
|---|---|---|---|---|---|---|---|
| Lateral ventricles | | | | | | | A versus B versus C,[a] A versus C,[b] B versus C,[a] A versus B[c] |
| Normal | 35 | 56 | 7 | 29 | 33 | 79 | |
| Questionable | 16 | 26 | 9 | 38 | 8 | 19 | |
| Abnormal | 11 | 18 | 8 | 33 | 1 | 2 | |
| Third ventricle | | | | | | | B versus C[b] |
| Normal | 45 | 72 | 17 | 70 | 35 | 83 | |
| Questionable | 11 | 18 | 3 | 13 | 7 | 17 | |
| Abnormal | 6 | 10 | 4 | 17 | 0 | 0 | |
| Frontal/parietal cortex | | | | | | | A versus B versus C,[c] A versus C[b] |
| Normal | 47 | 76 | 18 | 75 | 39 | 93 | |
| Questionable | 14 | 22 | 4 | 17 | 2 | 5 | |
| Abnormal | 1 | 2 | 2 | 8 | 1 | 2 | |
| Medial temporal structures | | | | | | | A versus B versus C,[b] A versus C,[a] B versus C[b] |
| Normal | 35 | 56 | 12 | 50 | 33 | 79 | |
| Questionable | 16 | 26 | 9 | 37 | 9 | 21 | |
| Abnormal | 11 | 18 | 3 | 13 | 0 | 0 | |
| Global | | | | | | | A versus B versus C,[a] A versus C,[a] B versus C[a] |
| Normal | 21 | 33 | 6 | 25 | 24 | 57 | |
| Questionable | 22 | 36 | 8 | 33 | 16 | 38 | |
| Abnormal | 19 | 31 | 10 | 42 | 2 | 5 | |

[a] $p<0.01$.
[b] $p<0.05$.
[c] $p<0.10$.

**TABLE 3. Correlations of Pathomorphology Ratings for Brain Regions in 86 Schizophrenic Patients and 42 Normal Comparison Subjects**

| Brain Region | Correlation (r): Lateral Ventricles | Third Ventricle | Medial Temporal Structures |
|---|---|---|---|
| Frontal/parietal cortex | 0.28[a] | 0.27[a] | 0.20[b] |
| Lateral ventricles | | 0.44[a] | 0.50[a] |
| Third ventricle | | | 0.43[a] |

[a] $p<0.01$.
[b] $p<0.05$.

had consistently higher rates of pathomorphology, but the only difference that reached statistical significance was for the lateral ventricles (for male patients, 37% normal, 37% questionable, and 26% abnormal; for the female patients, 69% normal, 15% questionable, and 16% abnormal ($\chi^2$=8.3, df=2, p=0.02).

## DISCUSSION

Using blind qualitative assessment of MRIs, we detected rates of abnormal brain morphology that were comparable to rates reported in the literature for similar populations (3–15). The substantial number of questionable ratings indicates the difficulty in distinguishing subtle abnormalities in brain morphology from what may be extremes in normal human neuroanatomic variation. Almost all morphometric postmortem CT and MRI studies have found a considerable overlap between patients and control subjects, with the majority of patients having values within the control range. The percentage of patients having values outside the range of the control subjects varies from 5% to 40% and depends on the selection criteria used to ascertain patients and control subjects, the assessment methods, and the specific brain region evaluated.

Although there are arguments derived from statistical considerations of ventricular measure distributions which suggest that a subgroup of schizophrenic patients have abnormal values and also that the whole Gaussian distribution of VBR values is shifted toward higher values (5), there is no doubt that the brain structure of the majority of schizophrenic patients looks normal, or at least not definitely abnormal, whereas some patients clearly have enlarged ventricles. This qualitative study came to the same conclusion. Moreover, the very high correlations of our qualitative ratings with the actual volumes show that qualitative ratings, which are much less time consuming and easier to perform than morphometric procedures, can be a valuable tool in psychiatric evaluation if performed by trained physicians.

The most problematic structure to assess was the cerebral cortex. As in the medial temporal lobe, the configuration of cortical sulci and gyri in the normal human brain has enormous variability. Therefore, we were quite conservative (possibly overly cautious) in defining cortical structures as abnormal. Indeed, only three of the 86 schizophrenic patients were rated as having definitely abnormal cortices. Our experience and that of others reported in the literature derived from CT scan studies of schizophrenic subjects suggests that the percentage of schizophrenic subjects with definite enlargement of cortical sulci and fissures (including the Sylvian and interhemispheric fissures) is considerably higher (2). While coronal MRI scans are superior to CT in assessing the ventricles and various soft tissue structures, including medial temporal structures, axial CT or MRI scans might be more appropriate than the coronal slices that we used to rate cortical sulcal and fissure enlargement by qualitative visual inspection.

We found significant correlations in abnormal morphology between the lateral and third ventricles and the medial temporal structures. The lower correlations between the frontal/parietal cortex and the other regions could be seen as consistent with the hypothesis of independent pathological processes affecting different brain regions (cortical and subcortical), as suggested by Cannon et al. (25). In our schizophrenic groups there were many patients who had selective enlargement of the lateral and/or third ventricle or had abnormalities of the medial temporal structures or cortex, indicating the lack of neuropathological homogeneity of the disease (figure 1, C, and figure 3, B–D). However, any such interpretation is limited by the intercorrelation among brain regions and the low rates of abnormality in the cortical regions that we found in this study.

The fact that both schizophrenic groups had greater rates of abnormal morphology than the normal subjects but did not significantly differ from each other is interesting and has several implications. First, these results confirm previous findings of abnormal brain morphology in young schizophrenic patients at the onset and early stages of their illness (26–33) as well as in chronic patients (2, 3). The 31% prevalence of global abnormal morphology in the first-episode patients is less than the rates described in more chronic populations in the literature but is comparable to that of other first-episode samples. However, only one-third of the first-episode patients were rated normal and 36% were rated questionable. This raises the possibility that a larger proportion of schizophrenic patients at the onset of illness may exhibit pathological changes of the brain and that these may not only be seen in a subgroup of schizophrenic individuals but are more widely distributed, as has been suggested by Suddath et al. (5). The limiting factors in the latter case are the standards for comparison and methods of assessment.

Second, the fact that the rates of abnormal morphology were not substantially greater in the chronic patients than in the first-episode patients suggests that there is not substantial progression in the neuropathology of schizophrenia, at least of a magnitude that visual inspection can detect. This interpretation is further supported by the fact that the chronic patients were treatment refractory, so they not only were older and had been ill longer but also had a severe form of the illness. The greater proportion of male subjects in the chronic group is significant, because there are suggestions from our data and the data of others that male patients may have higher rates of abnormal morphology than female patients (6, 8, 9, 22, 34). On the other hand, it should also be pointed out that the chronic patients had generally higher rates of abnormal morphology and a greater frequency of multiple areas of involvement than the first-episode patients. However, the degree to which the chronic schizophrenic patients exhibited greater abnormal morphology, though noteworthy, does not seem to be sufficiently great to be explained as reflecting progressive neuropathological change during the illness. Rather, it would seem to be due to the concentration of predominantly male patients with more severe forms of schizophrenia in the chronic group. This is consistent with prospective studies of brain morphology conducted with CT (35–38) and MRI (39, 40), the majority of which found no consistent pattern of change. We also cannot rule out the possibility that chronic exposure to treatment may be a factor in the differences in morphology between the patient groups. It is also possible that if neuropathological changes do occur in the course of the illness, they may be of a magnitude which was not detectable by visual inspection. Thus, both to answer the question of whether neuropathological change is progressive during the illness and to define more clearly the population exhibiting pathomorphology, valid and reliable methods of quantitative assessment are required (41–43).

**TABLE 4. Number of Abnormal and/or Questionable Ratings for Brain Regions Within Individual Schizophrenic Patients and Normal Comparison Subjects**

| | Schizophrenic Patients | | | | Normal Comparison Subjects (N=42) | |
|---|---|---|---|---|---|---|
| | First-Episode (N=62) | | Chronic (N=24) | | | |
| Number of Brain Regions/ Rating | N | % | N | % | N | % |
| No region | | | | | | |
| Abnormal | 43 | 69 | 14 | 58 | 40 | 95 |
| Abnormal/ questionable | 21 | 34 | 6 | 25 | 24 | 57 |
| One region | | | | | | |
| Abnormal | 10 | 16 | 6 | 25 | 2 | 5 |
| Abnormal/ questionable | 14 | 23 | 5 | 21 | 10 | 24 |
| Two regions | | | | | | |
| Abnormal | 8 | 13 | 2 | 8 | 0 | 0 |
| Abnormal/ questionable | 14 | 23 | 3 | 13 | 7 | 17 |
| Three regions | | | | | | |
| Abnormal | 1 | 2 | 1 | 4 | 0 | 0 |
| Abnormal/ questionable | 8 | 13 | 9 | 38 | 0 | 0 |
| Four regions | | | | | | |
| Abnormal | 0 | 0 | 1 | 4 | 0 | 0 |
| Abnormal/ questionable | 5 | 8 | 1 | 4 | 1 | 2 |

It seems clear that given the substantial overlap between patients and comparison subjects on measures of brain morphology, and until the diagnostic specificity of the characteristic forms of pathomorphology is established, brain MRI will not be useful in determining the diagnosis of schizophrenia apart from ruling out the occurrence of other neurological conditions (e.g., obstructive hydrocephalus, tumor, cerebrovascular infarction). However, evidence is emerging which associates abnormal brain morphology with forms of schizophrenia that have poorer prognoses (44, 45, and unpublished paper by J. Lieberman et al.). The most consistent finding has been that patients with abnormal morphology respond less well to antipsychotic drug treatment and have a poorer outcome (29, 45, 46–49). The increased rate of abnormal morphology in the chronic patients in our study (though not statistically significant) is consistent with this. Thus, brain MRIs may provide useful information to clinicians for evaluating the prognosis and determining treatment strategies for patients. For example, if patients with abnormal morphology take longer to respond to antipsychotic drugs and have a greater likelihood of ultimately being unresponsive, clinicians may want to allow a longer trial for a given dose or type of medication before changing the regimen. This could be particularly useful in limiting the potential for drug toxicity that can occur when drug dosage is increased too rapidly and unnecessarily. It could be particularly useful with younger patients who are earlier in their course of illness or with patients whose prior histories are not well known to the clinician.

In summary, qualitative evaluations of brain morphology on MRI scans by trained observers under blind conditions were able to identify abnormal morphology in first-episode and chronic schizophrenic patients as compared to normal subjects at rates that were comparable to those reported in the literature for these populations. The fact that only moderately higher rates of pathomorphology were seen in chronic multiepisode than in first-episode schizophrenic patients suggests that preexisting brain pathology may predispose to more severe forms of the illness rather than reflect a progressive or degenerative process.

Despite its limits in sensitivity, and until quantitative morphometric techniques are more practical and more widely available, qualitative assessment of brain morphology appears to be a useful technique in research and clinical evaluation of patients with schizophrenia.

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## APPENDIX 1. Criteria for Qualitative Assessment of Brain Morphology

### LATERAL VENTRICLES

*Abnormal*

1. Extreme blunting of the lateral angles of the lateral ventricles at the central part or frontal horns, or
2. Extreme size of the lateral ventricles in two of three sections (frontal, body, and occipital), or
3. Any three of the following:
   Moderate blunting of the lateral angles of the lateral ventricles at the central part and frontal horns
   Moderate size of the lateral ventricles in at least two of three sections (frontal, body, and occipital)
   Marked asymmetry in size of the right and left lateral ventricles
   Markedly abnormal shape of the lateral ventricles

*Questionable*

1. Any two of the following:
   Moderate blunting of the lateral angles of the lateral ventricles at the central part and frontal horns
   Moderate size of the lateral ventricles in two of three sections (frontal, body, and occipital)
   Moderate asymmetry in size of the right and left lateral ventricles
   Moderately abnormal shape of the lateral ventricles

### THIRD VENTRICLE

*Abnormal*

1. Marked widening of the third ventricle, particularly in the anterior portion

*Questionable*

1. Moderate widening of the third ventricle throughout its anteroposterior extent

### CORTEX

*Abnormal*

1. Marked enlargement of the cortical sulci in the anterior, parietal, or occipital lobe, or
2. Any two of the following:
   Marked enlargement of the interhemispheric fissure

Marked enlargement of the cortical subarachnoid space
Marked enlargement of the subarachnoid cisterns

*Questionable*

1. Diffuse and moderate enlargement of cortical sulci in the anterior, parietal, or occipital lobe
2. Any two of the following:
   Moderate enlargement of the interhemispheric fissure
   Moderate enlargement of the cortical subarachnoid space
   Moderate enlargement of the subarachnoid cisterns

MEDIAL TEMPORAL LOBE

*Abnormal*

1. Marked abnormality in the shape of the hippocampus (loss of the gyral pattern, reduction in size, abnormal shape), or
2. Marked enlargement of the temporal horn plus at least a moderate abnormality in the shape or size of the hippocampus, or
3. At least a moderate rating on 1 or 2 plus the following:
   Marked reduction in the size of the hippocampus
   Extreme asymmetry of the shape or size of the hippocampus or temporal horn

*Questionable*

1. Any two of the following:
   Moderate reduction in the size of the hippocampus
   Moderate enlargement of the temporal horn plus at least a moderate abnormality in the shape or size of the hippocampus
   Moderate asymmetry of the shape or size of the hippocampus or temporal horn

# Pattern of Recurrence of Illness After Recovery From an Episode of Major Depression: A Prospective Study

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*Objective: This study assessed prospectively the pattern of recurrence of illness after recovery from an episode of major depression. Method: Seventy-two patients who had recovered from an episode of primary, nonbipolar, nonpsychotic major depression were evaluated bimonthly with the Comprehensive Psychopathological Rating Scale for a period ranging from 20 to 108 months (median=66 months). New ("prospective") episodes were ascertained with a structured diagnostic interview. The probabilities of remaining well after the index episode and after the first prospective episode were assessed by the life-table method. The severity and duration of prospective episodes and the index episode were compared by linear regression analysis. Results: The probability of remaining well after recovery from the index episode was 76% at 6 months, 63% at 1 year, and 25% at 5 years. The risk of recurrence was lower among patients receiving prophylactic treatment with antidepressants and/or lithium and among those with histories of fewer than three previous episodes. The probability of remaining well was significantly lower 2 years after the first prospective episode than 2 years after the index episode. A pattern of increasing severity from the index episode to the first, second, and third prospective episodes was observed and was not affected by treatment. Conclusions: Major depression has a high rate of recurrence, even when bipolar and psychotic cases are excluded. The highest rate is observed during the first months after recovery from an episode. Prophylactic drug treatment reduces the risk of recurrence but apparently does not affect the trend toward increasing severity of subsequent episodes.*

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The pattern of recurrence of illness after recovery from an episode of major depression has been repeatedly investigated during the last decade with the use of quantitative survival analysis techniques (1–6). Most studies have focused on the time between recovery and the first prospectively observed new episode ("prospective" episode), showing that the longer individual patients stay well after the index episode, the less likely they are to experience a recurrence. Only a few papers have reported on the time to the second prospective episode, showing that it tends to be shorter than the time to the first prospective episode (2).

The above-mentioned data have been obtained by longitudinal follow-up of groups of patients whose treatment was not under the researchers' control. In most investigations, however, the assessment of the course of illness was actually done retrospectively, by reviewing, on the basis of information provided by the patients, periods as long as 6 months. The validity of the findings obtained by this procedure has been questioned (7).

Other shortcomings of some of the currently available studies include 1) imprecise definition of "recovery" (in order to be complete, a definition should specify a threshold for the number and severity of symptoms and indicate the period for which the symptoms must remain at a subthreshold level); 2) confusion between the concepts of recurrence (a new episode that occurs after recovery from the index one) and relapse (a return of symptoms, satisfying the full criteria for an episode, that occurs during a period of remission but before actual recovery); 3) inclusion of patients with bipolar illness in the patient groups studied (this may confuse the picture, since patients with bipolar disorder have been reported to be at higher risk for recurrence than patients with unipolar disorder); and 4) failure to stratify patients according to the treatment received during the observation period (prophylactic medication with antidepressants or lithium is likely to affect the course of

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illness, although it must be acknowledged that the choice of treatment is itself in part determined by the clinical situation).

These methodological drawbacks may help explain the divergent findings reported in the literature concerning factors that affect the risk of recurrence. A predictive value of the number of previous episodes has been detected by some authors (1, 5) but not confirmed by others (6), and the same applies to the predictive significance of an underlying minor depression (2, 5) and of the persistence of nonsuppression of cortisol on the dexamethasone suppression test (DST) after recovery from the index episode (8).

In this article we report on a study in which patients who had recovered from an episode of primary, nonpsychotic major depression, and who had no previous history of mania or hypomania, were followed up for a period of 20–108 months by means of bimonthly personal interviews. We evaluated 1) the time to the first and second prospective recurrences, 2) the factors affecting the risk of recurrence at 2, 3, and 5 years after recovery from the index episode, 3) the stability of diagnosis during the observation period, 4) the severity and duration of prospective episodes as compared to the index episode, and 5) the pattern and prognostic significance of symptoms between episodes.

## METHOD

Subjects were recruited from a center for affective disorders at the University of Naples. All patients who recovered from an episode of primary, nonpsychotic major depressive disorder, defined according to the Research Diagnostic Criteria (RDC) (9), between Jan. 1, 1982, and Dec. 31, 1983, and who had no history of mania or hypomania were admitted to the study. Recovery was defined as 1) the absence, for at least 8 consecutive weeks, of the prominent dysphoric mood required by RDC criterion A for major depressive disorder and 2) the presence, during the same period, of no more than two symptoms listed in criterion B for major depressive disorder, each with a rating of no more than 1 on the Hamilton Rating Scale for Depression (10). The RDC diagnosis was made after the patient had been interviewed with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (11). All interviews were conducted and all diagnoses were made by the same senior psychiatrist (M.M.), who had received formal training in the use of the RDC and the SADS within the framework of his collaboration with the World Health Organization and had had long experience in the application of these instruments in research settings.

The study group included 72 patients (30 male and 42 female) whose age at entry ranged from 27 to 55 years (mean=42.3 years, SD=6.6) and whose education level ranged from 2 to 17 years (mean=9.6 years, SD=3.6). Forty-seven patients (65.3%) were married, 17 (23.6%) had never been married, six (8.3%) were separated or divorced, and two (2.8%) were widowed. The mean age at onset of the first RDC major depressive episode was 32.6 years (SD=5.6). The index episode was the first RDC major depressive episode for six patients (8.3%), whereas 23 patients (31.9%) had had one or two previous episodes, and 43 (59.7%) had had three or more previous episodes. Eighteen patients (25.0%) had family histories of RDC major affective disorders (determined by using the Family History Research Diagnostic Criteria) (12). Forty-five patients (62.5%) were hospitalized for the index episode, and 27 (37.5%) were not. The mean duration of the index episode was 2.8 months (SD=1.9). The mean score on the Hamilton depression scale at the height of the episode was 21.8 (SD=3.3). According to the RDC, the index episode was of the endogenous type in 21 patients (29.2%); the episode was superimposed on a chronic and intermittent minor depressive disorder in 19 patients (26.4%) and on a cyclothymic personality in seven (9.7%). For 69 patients, the DST could be performed after recovery from the index episode (for methods, see reference 13). Nonsuppression was detected in 11 patients (15.3%).

All patients were instructed to visit the center bimonthly for clinical assessment. Treatment was decided by the psychiatrist in charge of each patient and was not under the control of the investigators. On each visit, patients were evaluated with the Comprehensive Psychopathological Rating Scale (14). The occurrence of RDC-defined major depressive, manic, schizoaffective, or schizophrenic episodes was ascertained by using the relevant sections of the SADS, and this information was recorded. If the patient was hospitalized, assessments were performed on the hospital ward. Recovery from the prospective episodes was defined by the same criteria that were used for recovery from the index episode. All interviews were conducted and all diagnoses were made by the same senior psychiatrist (R.P.), who was blind to the baseline information. He had received formal training in the use of the RDC, the SADS, and the Comprehensive Psychopathological Rating Scale, and his consistency with the initial rater (M.M.) in the application of each of these instruments had been formally assessed and found to be satisfactory (90% agreement or greater).

The duration of the observation period ranged from 20 to 108 months (median=66 months); it was 3 years or more for 64 patients (88.9%) and 4 years or more for 55 (76.4%). During this period, 53 patients (73.6%) received prophylactic medication with tricyclic antidepressants (at least 75 mg/day) or lithium carbonate (at least 600 mg/day) or both, whereas 19 patients (26.4%) received lower doses of these drugs or were not given prophylactic treatment. These two subgroups of patients did not differ significantly with respect to duration and severity of the index episode and number of previous episodes.

The probability of remaining well after recovery from the index episode was estimated at 2-month intervals up to 5 years by the life-table standardized method (15). The same method was used to obtain survival curves for patient subgroups defined by treatment received (no prophylactic treatment versus prophylactic treatment with tricyclic antidepressants, lithium, or both), number of previous episodes (three or more versus fewer than three), and whether or not the index episode was superimposed on a chronic and intermittent minor depressive disorder. Curves were compared by the Mantel-Haenszel test (15). An additional estimate obtained for the entire patient group, as well as for the subgroups, was the monthly rate of episodes (number of episodes per number of person-months observed) for the whole observation period and for each year of follow-up.

Stepwise multivariate logistic regression was used to analyze the effect of several variables on the risk of recurrence at 2, 3, and 5 years after the index episode. Variables included sex, age, education level, marital status, age at onset of illness, number of previous episodes, family history of major affective disorders, inpatient or outpatient status during the index episode, duration of the index episode, score on the Hamilton depression scale at the height of the index episode, RDC subtype of the index episode, presence or absence of an underlying chronic and intermittent minor depressive disorder or cyclothymic personality, and response on the DST at entry.

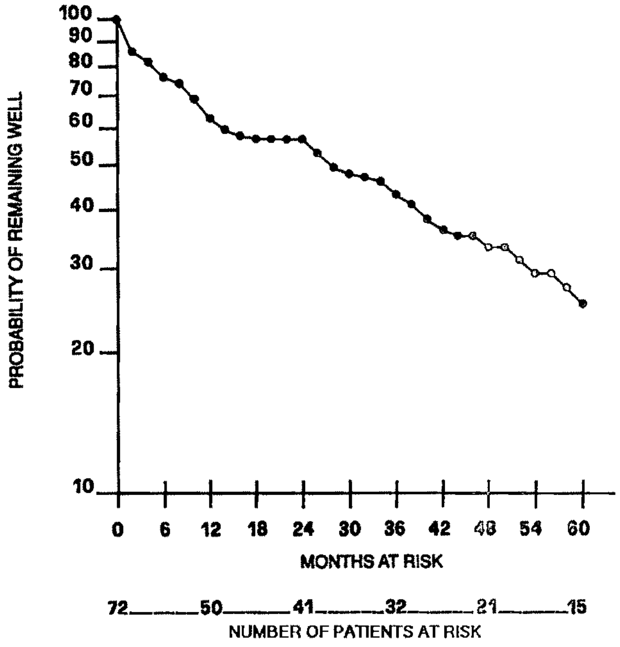
For the 51 patients who experienced a recurrence, the probability of remaining well after the first prospective episode (at 2-month intervals up to 3 years) was assessed by the life-table standardized method. For these patients, the cumulative probability of remaining well after recovery from the first prospective episode was compared with that after recovery from the index episode by using the Mantel-Haenszel test. Linear regression analysis was used to compare the severity and duration of the first, second, and third prospective episodes with that of the index episode. The same analysis was performed for the patient subgroups defined by treatment received.

Finally, the relation between the occurrence of each symptom on the Comprehensive Psychopathological Rating Scale during intervals between episodes and the risk of a recurrence in the subsequent year was evaluated by stepwise multivariate logistic regression.

## RESULTS

During the observation period, we recorded 120 episodes in the 51 patients with recurrences. The RDC diagnosis was nonpsychotic major depression in 97 episodes (80.8%), psychotic major depression in 13 (10.8%), mania in six (5.0%), schizoaffective disorder in three (2.5%), and schizophrenia in one (0.8%). Twenty-one (29.2%) of the 72 subjects did not have any episode during the observation period (which, for them, ranged from 38 to 96 months, with a median 64 months). Thirty-four patients (47.2%) had only episodes of nonpsychotic major depression, six (8.3%) had episodes of both nonpsychotic and psychotic major depression, five (6.9%) had episodes of both nonpsychotic major depression and mania, and three (4.2%) had only episodes of psychotic major depression. One patient had episodes of both nonpsychotic major depression and schizoaffective disorder, one had episodes of both psychotic major depression and schizoaffective disorder, and one had both schizoaffective and schizophrenic episodes.

**FIGURE 1. Cumulative Probability of Remaining Well for 72 Patients After Recovery From the Index Episode of Major Depression**



The cumulative probability of remaining well after recovery from the index episode was 86% at 2 months, 76% at 6 months, 63% at 1 year, 57% at 2 years, 43% at 3 years, and 25% at 5 years. A 50% probability was detected at 2 years and 4 months after recovery (figure 1). A significant difference in the probability of remaining well after recovery from the index episode was observed between patients who received prophylactic treatment and those who did not ($\chi^2=12.70$, df=1, $p<0.001$, Mantel-Haenszel summary) (figure 2) and between patients with three or more previous episodes and those with fewer than three episodes ($\chi^2=3.84$, df=1, $p<0.05$, Mantel-Haenszel summary) (figure 3). The difference between the survival curves of the patients with and the patients without an underlying chronic and intermittent minor depressive disorder was not significant ($\chi^2=1.99$, df=1, $p>0.10$, Mantel-Haenszel summary).

The monthly rate of episodes was 5% (declining from 7% in the first year of observation to 3% in the fifth year) in the entire patient group, 4% in treated patients, 9% in untreated patients, 3% in those with fewer than three previous episodes, and 7% in those with three or more previous episodes.

On stepwise multivariate logistic regression, the risk

FIGURE 2. Cumulative Probability of Remaining Well After Recovery From the Index Episode of Major Depression for 53 Patients Receiving and 19 Patients Not Receiving Prophylactic Drug Treatment

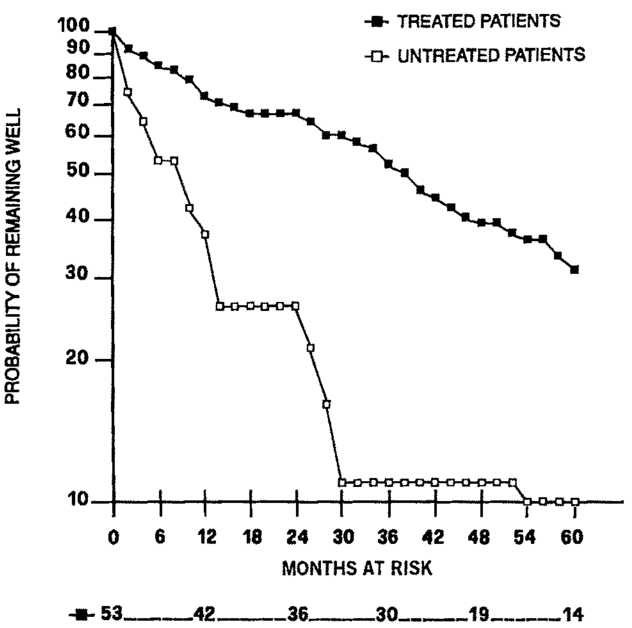
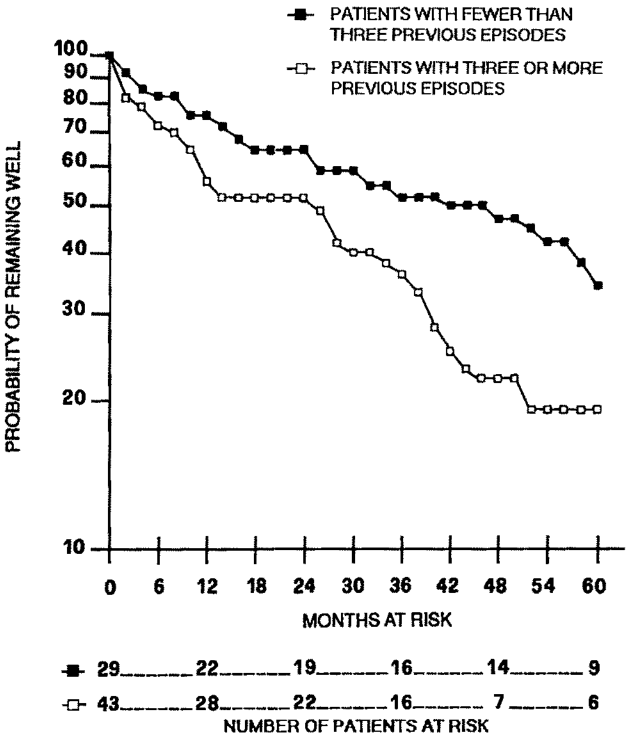


FIGURE 3. Cumulative Probability of Remaining Well After Recovery From the Index Episode of Major Depression for 29 Patients With Fewer Than Three and 43 Patients With Three or More Previous Episodes



of recurrence at 2 and 3 years after recovery from the index episode was found to be affected only by the number of previous episodes (at 2 years, F=11.82, df=1, 64, $p<0.0001$; at 3 years, F=21.14, df=1, 58, $p<0.0001$), whereas the risk of recurrence at 5 years was affected by the number of previous episodes (F=15.01, df=1, 41, $p<0.0001$), by the presence of an underlying chronic and intermittent minor depressive disorder (F=12.24, df=2, 40, $p<0.0001$), and by a family history of major affective disorders (F=11.84, df=3, 39, $p<0.0001$).

For the 51 patients who experienced a recurrence, a 50% probability of remaining well after recovery from the first prospective episode was detected at 22 months. For these patients, the probability of being well was significantly lower 2 years after the first prospective episode than 2 years after the index episode ($\chi^2=4.23$, df=1, $p<0.05$, Mantel-Haenszel summary), whereas differences were not significant with respect to probabilities at 1 and 3 years.

On linear regression analysis, a pattern of increasing severity from the index episode to the first, second, and third prospective episodes was observed (F=13.74, df=1, 67, $p<0.0004$). The same pattern was found in the subgroup of patients who received prophylactic treatment (F=6.14, df=1, 56, $p<0.01$). No significant pattern in duration of the episodes was found.

During the observation period, we recorded at least one between-episodes symptom on the Comprehensive Psychopathological Rating Scale in 818 (38.0%) of 2,153 follow-up visits. The most frequently rated symptoms during the first 5 years of observation were lassitude (58.3% of patients and 8.7% of visits), sadness (50.0% of patients and 5.5% of visits), and reduced sleep (34.7% of patients and 4.3% of visits). Only four patients (5.5%) did not have any between-episodes symptom on the Comprehensive Psychopathological Rating Scale during the entire observation period (ranging, for them, from 42 to 60 months); all four of them were also free of prospective episodes. On stepwise multivariate logistic regression, the only between-episodes symptom on the Comprehensive Psychopathological Rating Scale whose occurrence was significantly associated with the risk of recurrence during the subsequent year was pessimistic thoughts (F=6.00, df=1, 110, $p<0.01$).

## DISCUSSION

The main strengths of this study are the following. 1) All patients were evaluated bimonthly by means of personal interviews throughout the follow-up period, so that the course of illness was directly observed rather than retrospectively reviewed on the basis of information provided by the patients (in particular, the assessment of the nature, duration, and severity of prospective episodes was as direct and accurate as that of the index episode). 2) Clear definitions of episode and recovery, based on the RDC and perfectly corresponding to those recently proposed by Frank et al. (16), were used, and attention was focused on recurrences (new episodes occurring after recovery) as opposed to relapses (returns of symptoms before recovery). 3) In the follow-up period, all of the interviews were done and all of the diagnoses were made by the same psychiatrist (thus eliminating the bias involved in changing the assessor from one patient to another or in changing the assessor for the same patient through a period which in some cases was as long as 9 years). 4) The psychiatrist who conducted all interviews and made all diagnoses during follow-up was blind to the baseline information on the patients, so that the expectations of the investigators did not affect the research findings.

The main limitation of the study is that it was carried out in a specialized university center, to which the most severe cases are especially likely to be referred. A reflection of this fact can be found in the percentage of first-episode patients, which was much lower even than that reported in studies conducted in similar university settings in the United States (2), suggesting that selection bias may be more pronounced in geographic areas (such as southern Italy) where very few specialized research centers are available. Because of this bias, the results of the study cannot be generalized to the entire population of patients with major depressive disorder.

Overall, this investigation confirmed that major depression has a high rate of recurrence, even when bipolar and psychotic cases are excluded. Within a period of 5 years, three of four patients who have recovered from a major depressive episode can be expected to undergo a recurrence. This figure is consistent with the estimate of the NIMH/NIH Consensus Development Conference Statement (17), according to which "between 50% and 85% of patients with a major depressive episode who seek treatment at university medical centers will have at least one subsequent episode of depression in their lifetime." It was also confirmed that the risk of recurrence is highest during the first months after an episode and decreases the longer the patient continues to stay well. This calls for careful monitoring and continuous treatment of patients who have just recovered from an episode of major depression. On the other hand, the tendency toward a decrease in the probability of remaining well after the first prospective episode was only partially verified; in particular, the probability was reduced at 2 years but not reduced at 1 year and 3 years.

A history of three or more major depressive episodes was found to be the most powerful predictor of an early recurrence after recovery from the index episode, whereas the evidence concerning the predictive value of the presence of an underlying minor depressive disorder was equivocal (the comparison between the survival curves of patients with and without this underlying disorder showed no significant difference, but the presence of the disorder was associated with a high risk of recurrence at 5 years after recovery from the index episode). The finding of a prognostic value of persisting nonsuppression of cortisol on the DST was not replicated. In this connection, it is important to emphasize that previous studies which reported this finding did not adequately define "recovery" from the index episode, so that persisting nonsuppression may have been related to incomplete remission of symptoms.

The impact of prophylactic treatment on the risk of recurrence in patients who have recovered from an episode of major depression is evident from our data. We recognize that in a naturalistic study, "treatment itself becomes an outcome, because the patient's state [is] likely to help determine the choice of treatment" (18). Nevertheless, since our patients who received prophylactic treatment did not differ significantly from those who did not receive it with respect to the duration and severity of the index episode and the number of previous episodes, we assume that the therapeutic habits of the psychiatrists in charge of the patients, and the patients' own attitudes toward treatment, were the main determinants of medication status in our study group, so that stratification of patients by treatment received is correct and useful.

If prophylactic treatment affects the risk of recurrence, it does not seem, however, to influence the severity of prospective episodes. In fact, a trend of increasing severity from the index episode to the first, second, and third prospective episodes was observed in both treated and untreated patients. This finding suggests that the prognosis of nonpsychotic major depression is worse than currently believed, even when adequate drug treatment is provided, and may call for more comprehensive, multimodal therapeutic strategies. The occurrence of psychotic and schizoaffective episodes during the observation period points in the same direction and suggests an overlap between nonpsychotic major depression on the one hand and psychotic major depression and schizoaffective disorder on the other. Moreover, the appearance of a schizophrenic episode in one of our patients confirms that "sequential schizoaffective disorder" (19), i.e., a disorder marked by the independent occurrence of affective and schizophrenic episodes in the same individual, is a possible, although rare, phenomenon.

This study confirmed that symptoms between episodes are frequent in patients who have recovered from an episode of major depression. We suggest that these symptoms, when they do not reflect an underlying personality disorder, may have at least three different meanings: they may be the prodrome of a new episode, they may be residual symptoms after an episode, or they may represent a "micro-episode" in themselves. In individual patients, specific symptoms may be more often prodromic, residual, or part of a micro-episode, but no generalization is possible. Apparently, there are symptoms whose occurrence is associated with an increased risk of recurrence during the subsequent year. This was true in this investigation for the Comprehensive Psychopathological Rating Scale symptom of pessimistic thoughts (defined as fluctuating or persistent thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin). To relate this finding to cognitive models of depression is tempting but too speculative at this stage.

In conclusion, we believe that the investigation of the long-term course of nonpsychotic major depression can benefit greatly from the prospective follow-up of patients consecutively recruited and interviewed personally at short intervals and from the application of quantitative survival analysis techniques. Further research should, in our opinion, more thoroughly explore the influence of stressful events and social support on the course of illness, complementing the assessment of psychopathological status with the evaluation of psychosocial adjustment.

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# Lithium, Benzodiazepines, and Sexual Function in Bipolar Patients

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*Objective: Lithium and benzodiazepines are widely used in the treatment of bipolar patients. Yet studies of the effect of these drugs on sexual function are scarce. This study surveyed sexual function in bipolar patients treated with lithium, either alone or in combination with other drugs. Method: Sexual function was assessed by self-rating scale in 104 outpatients (45 men and 59 women) with a* DSM-III *diagnosis of bipolar disorder who were attending an affective disorders clinic. All patients were under treatment with lithium, either alone (35%) or in combination with benzodiazepines (49%), tricyclic antidepressants (17%), neuroleptics (17%), tryptophan (10%), or carbamazepine (1%). The patients were in a stable and euthyroid state at the time of the assessment. Serum lithium and plasma prolactin concentrations were measured at the same time. Results: Multiple regression analysis revealed an association between concomitant benzodiazepine administration and sexual dysfunction scores. Difficulties in sexual functioning were significantly more common in patients treated with a combination of lithium and benzodiazepines (49%) than in those treated with either lithium alone (14%) or lithium in combination with other drugs (17%). No relationship was found between serum lithium or plasma prolactin levels and sexual dysfunction scores. Conclusions: Lithium, when given alone, did not appear to have a major effect on sexual function, whereas its combination with benzodiazepines was associated with sexual dysfunction in about half of the patients. More attention should be given to drug-induced sexual dysfunction, since its presence can have important consequences for clinical management and compliance.*

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Although a large number of manic-depressive patients are treated with lithium, reports in the literature concerning the effects of lithium on sexual function are scarce (1), conflicting, and primarily anecdotal. Whereas in one study (2), decreased libido was reported in 50% of patients receiving long-term lithium treatment, other investigators have found this effect to occur in less than 5% of patients (3, 4). Impairment in sexual functioning during long-term lithium treatment has been reported in a small percentage of patients (3, 4) or has been reported to be absent (2). In two case reports of sexual dysfunction associated with lithium treatment in male patients with bipolar I disorder, the effect disappeared with placebo substitution in one patient, while in the other there was a spontaneous remission during continued treatment (5). A comparison of sexual functioning in 24 patients with major affective disorder treated with lithium and in a control group of surgical outpatients failed to reveal any significant differences between the groups in the prevalence of sexual dysfunction (6). Little information is available from these studies on the effect of medications given with lithium on sexual function. The inhibiting effect of benzodiazepines on sexual function has previously been reported (7–9). Most of these reports, however, are either anecdotal or based on animal studies. Literature on the effect of benzodiazepines on large samples of bipolar patients is rare.

The mechanism of action of psychotropic medications on sexual function is not well understood. Three different mechanisms may be involved: 1) central: the drug effect at the CNS level may cause sedation and subsequent inhibition of sexual activity, 2) peripheral: this effect may lead to blockade of cholinergic and α-adrenergic receptors of the autonomic nervous system, which will interfere with sexual function, and 3) hormonal: this effect may appear in the form of hyper-

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**TABLE 1. Lithium Dose and Serum Lithium and Plasma Prolactin Levels in Male and Female Bipolar Patients**

| | | Lithium | Serum Lithium | | Plasma Prolactin | |
|---|---|---|---|---|---|---|
| Group and Variable | N | Dose (mg/day) | N | Level (meq/liter) | N | Level (ng/ml)[a] |
| Men | 45 | | 42 | | 43 | |
| Minimum | | 450 | | 0.17 | | 3.2 |
| Maximum | | 2100 | | 1.49 | | 48.0 |
| Mean | | 1080 | | 0.61 | | 8.30 |
| SD | | 269 | | 0.22 | | 6.67 |
| Women | 59 | | 56 | | 58 | |
| Minimum | | 300 | | 0.14 | | 4.4 |
| Maximum | | 1500 | | 1.05 | | 77.0 |
| Mean | | 943 | | 0.58 | | 15.10 |
| SD | | 296 | | 0.18 | | 16.03 |

[a] Normal range for men=0–10; normal range for women=0–20.

prolactinemia or reduced androgen action and elevated estrogen levels in men. None of these possible mechanisms has been clearly identified as being associated with the effect of lithium on sexuality.

In view of the scarcity and inconclusive nature of the data with respect to lithium and sexual functioning, we carried out a survey of sexual functioning in manic-depressive outpatients treated with lithium, either alone or in combination with other psychotherapeutic drugs, of which the most frequent were the benzodiazepines. The data collected allowed us to explore the relationships among lithium dose, serum lithium levels, plasma prolactin levels, concomitant medications, and self-assessments of sexual dysfunction.

## METHOD

Patients were recruited for this study from an affective disorders clinic. All patients attending the clinic were asked to participate in the study, and those who agreed gave written informed consent. The group studied consisted of 104 outpatients (45 men and 59 women) who had a *DSM-III* diagnosis of bipolar disorder and were under treatment with lithium. The patients ranged in age from 20 to 68 years (mean=45).

Thirty-six patients (35%) were being treated with lithium alone, and the remainder with a combination of lithium and one or more other drugs: 51 (49%) with benzodiazepines (43 of these with clonazepam at doses ranging from 0.5 to 12.0 mg/day [mean=2.2 mg/day]), 18 (17%) with tricyclic antidepressants, 18 with neuroleptics, 10 (10%) with tryptophan, one (1%) with carbamazepine, and one with a combination of estrogen and methyltestosterone. Of the 68 patients being treated with a combination of lithium and other medications, 43 were receiving one concomitant drug, 20 were receiving two concomitant drugs, and five were receiving three concomitant drugs. The duration of treatment with lithium varied from 1 month to 25 years (mean=6.7 years, median=6.0). Ninety percent (N=94) of the patients had been treated with lithium for 6 months or longer. Any comorbid medical condition that was noted was considered mild and stabilized or in remission at the time of the survey. Only 16 of the 104 patients were receiving nonpsychiatric medications, most of which were at low doses.

The patients were interviewed by the same psychiatrist, who completed Clinical Global Impression Scales of Depression and Mania (9-point scales), the Hamilton Rating Scale for Depression, and a rating scale for mania that consisted of five items assessing mania taken from the Inpatient Multidimensional Psychiatric Scale and four from the Brief Psychiatric Rating Scale. The ratings suggest that at the time of the interview, 96 patients (92%) had normal mood or nearly so, six (6%) were mildly depressed, two (2%) were moderately depressed, and none was manic.

At the same visit, the patients completed the self-rating scale for sexual dysfunction, in separate versions for men and women (10). The men's version of the scale includes nine items and a global assessment of sexual functioning, and the women's version includes six items, a global assessment of sexual functioning, and two items concerning menstrual changes. Each item was rated on a 4-point scale relative to a period of normal mood while the patient was not treated with lithium (0=no change, 1=mild change, 2=moderate change, 3=great change). The scale used was a revised version of a self-rating scale that we have shown to be valid and sensitive for the detection of changes in sexual function induced by neuroleptics (10).

Blood samples for the assay of serum lithium and plasma prolactin levels (11) were taken at the time the patient completed the rating scale for sexual dysfunction.

## RESULTS

The lithium doses and serum lithium and plasma prolactin levels in the patients who completed the rating scale for sexual dysfunction are summarized in table 1.

The distribution of scores for each item of the self-rating scale for sexual dysfunction is shown for male patients in table 2. To summarize, 58% of male patients reported no change in sexual functioning while taking medication, 23% mild changes, 9% moderate changes, and 9% great changes (item 10). Responses to individual items of the questionnaire revealed that the changes consisted of decreased sexual desire (43%), difficulty in getting or maintaining an erection (40%), decreased quality of orgasm (36%), and decreased quantity of ejaculate (32%). The majority of these changes were mild. Few men reported any increase in sexual desire (7%) or improvement in sexual functioning (11%).

The distribution of the sexual dysfunction and menstrual change scores for female patients is shown in table 3. On the global assessment item (item 9), 75% of women reported no change in sexual functioning, 5% mild changes, 5% moderate changes, and 15% great changes. Specific difficulties noted were decreased sexual desire (40%), decreased quality of orgasm (24%),

**TABLE 2. Changes in Sexual Function in 45 Male Bipolar Patients Taking Lithium and Other Medications**

| | Change While Taking Medication | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | None | | Mild | | Moderate | | Great | | Missing Data |
| Symptom | N | %[a] | N | %[a] | N | %[a] | N | %[a] | |
| Diminished sexual desire | 25 | 57 | 10 | 23 | 9 | 20 | 0 | 0 | 1 |
| Increased sexual desire | 41 | 93 | 2 | 5 | 1 | 2 | 0 | 0 | 1 |
| Difficulty getting erection | 27 | 60 | 12 | 27 | 4 | 9 | 2 | 4 | 0 |
| Difficulty maintaining erection | 28 | 62 | 10 | 22 | 4 | 9 | 3 | 7 | 0 |
| Decreased ability to have orgasm | 30 | 67 | 7 | 16 | 6 | 13 | 2 | 4 | 0 |
| Decreased quality of orgasm | 29 | 64 | 8 | 18 | 7 | 16 | 1 | 2 | 0 |
| Increased quality of orgasm | 40 | 89 | 5 | 11 | 0 | 0 | 0 | 0 | 0 |
| Decreased quantity of ejaculate | 30 | 68 | 8 | 18 | 3 | 7 | 3 | 7 | 1 |
| Increased quantity of ejaculate | 40 | 93 | 2 | 5 | 1 | 2 | 0 | 0 | 2 |
| Difficulty in sexual functioning | 25 | 58 | 10 | 23 | 4 | 9 | 4 | 9 | 2 |

[a] Percents are based on number of patients for whom data were available.

**TABLE 3. Changes in Menstruation and Sexual Function in 59 Female Bipolar Patients Taking Lithium and Other Medications**

| | Change While Taking Medication | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | None | | Mild | | Moderate | | Great | | Missing Data |
| Symptom | N | %[a] | N | %[a] | N | %[a] | N | %[a] | |
| Change in menstruation | 29 | 67 | 7 | 16 | 1 | 2 | 6 | 14 | 16 |
| Change in quantity of blood loss | 28 | 65 | 6 | 14 | 5 | 12 | 4 | 9 | 16 |
| Decreased sexual desire | 34 | 61 | 11 | 20 | 6 | 11 | 5 | 9 | 3 |
| Increased sexual desire | 45 | 76 | 3 | 5 | 6 | 10 | 5 | 9 | 0 |
| Decreased quality of orgasm | 42 | 76 | 6 | 11 | 3 | 6 | 4 | 7 | 4 |
| Increased quality of orgasm | 45 | 79 | 5 | 9 | 5 | 9 | 2 | 4 | 2 |
| Pain during orgasm | 56 | 97 | 1 | 2 | 0 | 0 | 1 | 2 | 1 |
| Decreased ability to have orgasm | 43 | 74 | 4 | 7 | 4 | 7 | 7 | 12 | 1 |
| Difficulty in sexual functioning | 44 | 75 | 3 | 5 | 3 | 5 | 9 | 15 | 0 |

[a] Percents are based on number of patients for whom data were available.

decreased ability to have orgasm (26%), and pain during orgasm (4%). In women who were still menstruating, 35% reported disturbances in menstruation. In contrast to the results for men, 24% of women reported increased sexual desire while taking medication, and 22% reported improved orgasms.

Table 4 shows the overall assessment of changes in sexual function (item 10 for men and item 9 for women) classified by treatment combination. The results for men and women were pooled, since they did not show any statistically significant ($p<0.05$) differences in this respect. When given alone, lithium was associated with sexual dysfunction in 14% of patients. In contrast, 60% of patients receiving the lithium-benzodiazepine combination reported some degree of sexual dysfunction.

Stepwise multiple linear regression analyses were carried out for each sex separately to see whether lithium dose, serum lithium level, plasma prolactin level, age, or any of the classes of concomitant psychoactive medications being taken (benzodiazepines, tricyclic antidepressants, neuroleptics, tryptophan, and carbamazepine) were related to the global scores for the assessment of sexual dysfunction (item 10 for men and item 9 for women). For this purpose the stepwise inclusion method was used, with a significance level of $p<0.15$ for entry and retention in the model. Each of the classes of psychoactive medication was entered as a dichotomous dummy variable coded 1 or 0 according to whether or not the medication was being taken at the time of the survey. Only benzodiazepine intake was found to be related ($p<0.15$) to the global sexual dysfunction scores, and this relationship was stronger in women than in men (men: $F=2.68$, $df=1, 37$, $p=0.11$, $R^2=0.07$; women: $F=12.50$, $df=1, 55$, $p<0.001$, $R^2=0.19$). No relationship ($p<0.15$) was found between the global scores for sexual dysfunction and age, lithium dose, serum lithium concentration, or plasma prolactin concentration in either sex. When the patients were classified according to concomitant benzodiazepine intake, 49% of those taking benzodiazepines reported some degree of sexual dysfunction on the global assessment item, compared to 17% of those not taking benzodiazepines ($p<0.001$, Fisher's exact probability test, two-tailed). Clonazepam was the most frequent (86%) benzodiazepine taken.

Following this finding of an association between combined lithium and benzodiazepine intake and the global assessment of sexual dysfunction, we carried out exploratory stepwise multiple linear regression analyses in each sex on the individual items of the self-rating scale for sexual dysfunction to identify which aspects of sexual functioning were affected. Because this involved carrying out 17 separate multiple regression analyses, we used a stricter criterion of $p<0.05$ for entry and re-

**TABLE 4. Overall Assessment of Sexual Dysfunction in 104 Male and Female Bipolar Patients by Medication Received**

| | | Difficulty in Sexual Function While Taking Medication | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | None | | Mild | | Moderate | | Great | | |
| Medication | Total | N | %[a] | N | %[a] | N | %[a] | N | %[a] | Missing Data |
| Lithium only | 36 | 31 | 86 | 4 | 11 | 0 | 0 | 1 | 3 | 0 |
| Lithium plus one other drug | | | | | | | | | | |
| Benzodiazepines | 26 | 10 | 40 | 4 | 16 | 4 | 16 | 7 | 28 | 1 |
| Neuroleptics | 10 | 8 | 80 | 1 | 10 | 0 | 0 | 1 | 10 | 0 |
| Tricyclic antidepressants | 6 | 4 | 67 | 1 | 17 | 1 | 17 | 0 | 0 | 0 |
| Tryptophan | 1 | 1 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lithium plus benzodiazepines plus one or more other drugs | | | | | | | | | | |
| Neuroleptics | 6 | 3 | 60 | 2 | 40 | 0 | 0 | 0 | 0 | 1 |
| Tricyclics | 7 | 5 | 71 | 1 | 14 | 0 | 0 | 1 | 14 | 0 |
| Tryptophan | 6 | 3 | 50 | 0 | 0 | 1 | 17 | 2 | 34 | 0 |
| Carbamazepine | 1 | 1 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tricyclics and neuroleptics | 2 | 2 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tricyclics and tryptophan | 3 | 1 | 33 | 0 | 0 | 1 | 33 | 1 | 33 | 0 |

[a] Percents are based on number of patients for whom data were available.

tention of terms in the model. Age, lithium dose, serum lithium level, plasma prolactin concentration, and concomitant medication type were included as explanatory variables. These analyses revealed that in men, concomitant benzodiazepine intake was associated with difficulty in getting an erection ($F=6.51$, $df=1, 39$, $p=0.01$, $R^2=0.14$), decreased quality of orgasm in some patients ($F=5.32$, $df=1, 39$, $p=0.03$, $R^2=0.12$), but improved quality of orgasm in others ($F=5.33$, $df=1, 38$, $p=0.03$, $R^2=0.12$). The only other significant ($p<0.05$) relationship detected among the specific symptoms in men was an association between increased libido and a high serum lithium level ($F=17.82$, $df=1, 38$, $p<0.001$) but a low lithium dose (negative relationship, $F=4.26$, $df=1, 38$, $p=0.05$, $R^2=0.33$); however, this finding should be balanced against the fact that only three of 44 men who responded to this question reported an increase in libido since beginning medication.

In women, benzodiazepine intake was associated significantly ($p<0.05$) with absence of change in quantity of menstrual blood loss ($F=4.12$, $df=1, 39$, $p=0.05$, $R^2=0.10$). The only other significant ($p<0.05$) relationship detected among the specific symptoms in women was an association between increased libido and low lithium dose ($F=5.16$, $df=1, 55$, $p=0.03$, $R^2=0.12$).

Age was not significantly ($p<0.05$) related to any of the sexual dysfunction items in either men or women.

## DISCUSSION

Mania and depression have different effects on human libido and sexual behavior. In view of the fact that hypersexuality is a common finding in manic episodes (and even paradoxically in some depressive states), it may be difficult for a bipolar patient to make an objective judgment of his or her sexual function while treated with lithium. Often these patients perceive their sexual excitement during the manic phase as a pattern of sexual function to be expected after improvement. On the other hand, patients with underlying depression and decreased libido may assume that it is the medication which perpetuates their sexual impairment. Indeed, many of these patients become noncompliant as a result of this misconception.

The results of the present study suggest that it is unlikely that lithium, when given alone, has a major effect on the sexual functioning of bipolar patients receiving long-term prophylactic therapy. Only 14% of 36 patients treated with lithium alone reported any sexual difficulties, and there was no significant relationship between serum lithium level or lithium dose and the scores for global sexual functioning. The majority of the changes in sexual function reported during treatment with lithium alone were of a mild nature. This is in conflict with some of the previous findings, particularly from studies of the effect of lithium on normal control subjects (12, 13), which concluded that lithium has an inhibitory effect on male sexual desire or behavior. However, the effect of lithium on healthy volunteers may not be the same as that on manic-depressive patients.

The most important finding from this study was that the majority of cases of sexual dysfunction reported were associated with concomitant benzodiazepine, largely clonazepam, intake. About 50% of the patients treated with a combination of lithium and benzodiazepines complained of some degree of sexual difficulty regardless of whether a third medication was present or not. The inhibition of sexual response with benzodiazepines has previously been reported (7–9, 14). Because all of the patients included in this study were receiving lithium, it is impossible to say from these results whether benzodiazepines alone or the lithium-benzodiazepine combination was the causal factor. There is also the possibility that lithium may potentiate the effect of benzodiazepines on sexual function. In men, reduced libido occurred in 43% of all those surveyed, and the multiple regression analyses revealed that concomitant benzodiazepine intake was specifically associated with difficulties in getting an erection and diminished quality of the orgasm. In women, no specific form of impairment in sexual functioning associated with benzodiazepines could be identified despite the fact that the relationship between concomitant benzodiazepine intake and the global assessment of sexual dysfunction was of greater statistical significance than in men. However, this failure to identify specific problems associated with concomitant benzodiazepines in women may be a limitation of the group size, and it should be noted that among all women surveyed, reduced libido was reported in 40%, decreased ability to have an orgasm in 26%, and decreased quality of orgasm in 24%. Furthermore, the sexual dysfunction associated with the lithium-benzodiazepine combination could not, in either sex, be linked to any unique pathological traits that distinguished patients who were receiving concomitant benzodiazepines from those who were not. Insomnia could have been a factor in benzodiazepine administration, but in the absence of other symptoms of importance, it did not constitute a significant psychopathological development.

Most research studies of drug effects on human sexual behavior involve men and rarely women. In our previous study of schizophrenic patients (10), we found that women were as vulnerable to the adverse effects of antipsychotic drugs as men. The results from the present study suggest that women with bipolar affective disorder treated with lithium and other drugs were slightly less at risk for sexual dysfunction than men. Menstrual changes since beginning medication were reported in approximately 35% of all women surveyed but could not be linked to any specific drug. On the other hand, concomitant benzodiazepine administration appeared to be associated with less change in quantity of menstrual blood loss since beginning medications.

There are a number of methodological issues that have an important bearing on the study of drug effects on sexual function. Among them, age, current state of mood, and the use of concomitant psychotropic medications are but a few variables that can have an important effect on the interpretation of the results. Many reports tend particularly to ignore the effects of concomitant medications on sexual function. Moreover, hypothyroidism caused by lithium can also affect sexual drive and behavior. In the present study, the patients were stable and in a euthyroid state at the time of their evaluation, with the exception of a few mild mood changes. In addition, no relationship was found between age and sexual dysfunction. Other factors that impede efforts to reconcile the conflicting results of different research studies are the lack of a standard nomenclature of sexual dysfunction and standard measurement instruments.

More research is warranted to explore the effects of psychotherapeutic drugs on human sexual function. One way to study further the apparent relationship between concomitant lithium-benzodiazepine treatment and sexual dysfunction observed here would be temporary withdrawal and subsequent readministration of each drug in turn. Changes in sexual functioning could thus be ascribed with some degree of certainty to one or other of the drugs or to their combination. Such a procedure would, however, need to be carried out in stable, euthymic patients with particular attention to ethical considerations.

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# Learned Helplessness and Urinary MHPG Levels in Unipolar Depression

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*Objective: Studies of the learned helplessness paradigm in laboratory animals show increased central noradrenergic activity following exposure to uncontrollable stressors. In clinical studies, depressed patients as a group report higher perceptions of helplessness and powerlessness. The authors examined the relationship between perceptions of powerlessness and noradrenergic activity in depressed patients. Method: Twenty drug-free patients (12 women and 8 men) meeting* DSM-III *criteria for major depressive disorder were given the Kobasa Hardiness Questionnaire, which contains subscales measuring feelings of powerlessness, security, and alienation. Concurrently, 24-hour urine samples were collected for measurement of urinary MHPG. Results: Significant correlations were found between MHPG levels and total hardiness scores as well as between MHPG levels and total powerlessness scores but not between MHPG levels and total security or total alienation scores. Conclusions: These results suggest that depressed patients with high urinary output of MHPG are more likely to show the cognitive features of learned helplessness.*

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Since the initial report of Overmier and Seligman (1), numerous studies have confirmed and refined the learned helplessness phenomenon in laboratory animals. The standard laboratory paradigm exposes animals to uncontrollable and unpredictable stressors such as foot shock or noise in a pretest session. This is followed by a test session in which animals must learn to perform a response such as shuttle avoidance or lever press to terminate a stressor. In general, animals exposed to uncontrollable stressors show persistent deficits in performing the avoidance response. Seligman (2) has proposed that through exposure to the initial uncontrollable and unpredictable stressor, the animals learn that outcome is independent of response. This learning may then become generalized so that subjects respond with inactive behaviors or "helplessness" in the presence of future stressors.

The majority of laboratory studies support the notion suggested by Garber et al. (3) that exposure to uncontrollable and unpredictable stressors results in decrements in the spheres of motivation, cognition, and emotion that parallel certain symptoms associated with depressive disorders in clinical populations (3–5). Of importance, motivational decrements in animals exposed to uncontrollable stressors have been shown to be prevented by pretreatment with antidepressants (6–8) and reversed following treatment with imipramine (9) or nortriptyline (10). Hence, the learned helplessness paradigm has been suggested as an animal model for certain types of depressive disorders.

In animals, learned helplessness is associated with a higher rate of release of norepinephrine in the brain, as reflected by higher levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in whole brain (11, 12) and lower norepinephrine levels in a variety of brain regions (13, 14). These findings correspond to clinical observations that the onset of major depressive illness is often associated with exposure to stressors (15) and that certain subtypes of depressive disorders are associated with alterations in catecholaminergic neurotransmitter functioning (16–20). Of relevance, patients with depressive illnesses show heterogeneity with regard to urinary MHPG output, leading our group to suggest that patients with high MHPG output may have a distinct subtype of depressive illness (21).

In clinical studies, there is evidence that depressed patients, as a group, report perceptions of helplessness or powerlessness (22) and that these beliefs tend to decrease as the depressive illness improves. In this study, we ex-

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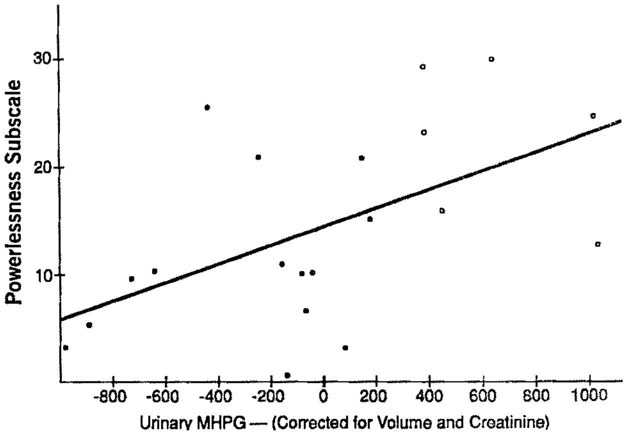
**TABLE 1. Correlations Between Scores on the Kobasa Hardiness Questionnaire and Urinary MHPG Levels in 20 Depressed Patients**

| | Correlation With MHPG | |
|---|---|---|
| Measure | r | p[a] |
| Total hardiness | –0.43 | 0.05 |
| Total alienation | 0.26 | n.s. |
| Total security | 0.38 | 0.09 |
| Total powerlessness | 0.46 | 0.04 |
| Powerlessness subscale derived from the Maddi Alienation Test | 0.51 | 0.02 |
| Rotter Internal-External Locus of Control Scale score | 0.28 | n.s. |

[a] Probability levels are two-tailed, df=18.

**FIGURE 1. Urinary MHPG Levels and Scores on the Kobasa Hardiness Questionnaire Powerlessness Subscale Derived From the Maddi Alienation Test in 20 Depressed Patients[a]**



[a] Urinary MHPG values were statistically adjusted for total volume and creatinine levels. The line running through the scattergram represents the line of best fit for the two variables (r=0.51, p=0.02).

amine the relationship between noradrenergic neuronal activity (as reflected by urinary MHPG levels) and perceptions of powerlessness in a group of hospitalized clinically depressed patients. Based on previous work from our laboratory and others, we hypothesized that higher levels of urinary MHPG would be associated with higher scores on measures of perceived powerlessness.

## METHOD

The patient sample consisted of 20 clinically depressed inpatients seen in two private psychiatric settings. For this study, we considered only those patients who were free from major medical disease and who showed no history of drug or alcohol abuse or addiction. A clinical *DSM-III* diagnosis of unipolar major depressive disorder and a minimum score of 18 on the Hamilton Rating Scale for Depression (21-item version) were required. The resulting sample consisted of eight men and 12 women who ranged in age from 17 to 57 years, with a mean of 31 years (SD=11). The mean Hamilton Depression Rating Scale score for the sample was 30 (SD=5).

On admission to the study, patients were asked to complete the Kobasa Hardiness Questionnaire (23), which includes the Rotter Internal-External Locus of Control Scale (24). One to three consecutive 24-hour urine samples were collected for determination of urinary MHPG and creatinine levels. MHPG levels were subsequently determined by using a modification of the method of Dekirmenjian and Maas (25), and creatinine levels were determined by using a modification of the Jaffe reaction. Biochemical determinations were performed by laboratory staff who were blind to the clinical data, and clinical information was obtained by staff blind to biochemical data. All patients had been free of psychoactive medication for at least 10 days before urine collections. Information on drug use for periods other than immediately prior to admission was not available and was not used in sample selection. Informed consent was obtained before all data collection procedures.

Pearson correlational analyses (two-tailed) were performed by using SPSS-X software. Perceptions were quantified first by using the total score from the Kobasa Hardiness Questionnaire calculated by summing z score equivalents from each of the components (26) and changing the sign so that a positive score indicated hardiness. Second, the total scores on each of the three scales making up the Kobasa Hardiness Questionnaire (i.e., alienation, security, and powerlessness) were examined separately by using the summed z scores of the scale components. Finally, the components making up the total powerlessness score were examined separately. As described by Kobasa et al. (26), these component scales included the powerlessness subscale derived from the Maddi Alienation Test and the Rotter Internal-External Locus of Control Scale. To correct for the effects of urine volume and creatinine on measures of urinary MHPG, urine volume and creatinine levels were statistically partialled from MHPG measures by using regression analysis, as recommended by Maes et al. (27).

## RESULTS

As shown in table 1, significant correlations were found between urinary MHPG levels and total hardiness scores as well as between urinary MHPG levels and total powerlessness scores but not between urinary MHPG levels and total alienation or total security scores. Examination of the components of the total powerlessness score showed a significant correlation between MHPG levels and scores on the powerlessness subscale derived from the Maddi Alienation Test but not between MHPG levels and scores on the Rotter Internal-External Locus of Control Scale. Figure 1 depicts the correlation between the powerlessness subscale derived from the Maddi Alienation Test and MHPG levels.

To control for the possibility that correlations were affected by age, sex, or severity of the depressive disorder, the data were analyzed statistically partialling for the effects of age, sex, and Hamilton Rating Scale for Depression score. Since one depressed subject refused to be scored on the baseline Hamilton Rating Scale for Depression, these analyses included only 19 of the 20 subjects. After statistical adjustments, the correlation between MHPG levels and total hardiness scores decreased in magnitude below significance levels (r=0.39, df=14, p=0.13) but significant correlations remained for the total powerlessness subscale (r=0.53, df=14, p=0.03) and for the powerlessness subscale derived from the Maddi Alienation Test (r=0.55, df=14, p= 0.03). As in the previous analyses, the subscale scores for total alienation and total security showed no significant correlation with MHPG levels.

## DISCUSSION

The results of the present study showed that the significant correlation between total hardiness scores and urinary MHPG levels was primarily influenced by a correlation between powerlessness scores on the Kobasa Hardiness Questionnaire and urinary MHPG levels. Further analyses showed that the association between MHPG levels and powerlessness was primarily influenced by the scores on the powerlessness subscale derived from the Maddi Alienation Test rather than the scores on the Rotter Internal-External Locus of Control Scale. The association found between perceptions of powerlessness and 24-hour urinary MHPG levels supports our initial hypothesis and provides a parallel for previous findings from our group showing an association between learned helplessness and higher brain levels of MHPG in animals (11, 12).

Although both the powerlessness subscale from the Maddi Alienation Test and the Rotter Internal-External Locus of Control Scale scale tap into perceptions of powerlessness, there are subtle differences between the two scales. The powerlessness subscale from the Maddi Alienation Test contains 15 items, seven of which concern the degree to which society in general or specific others control one's actions. In contrast, the Rotter Internal-External Locus of Control Scale contains 23 items, virtually all of which measure the degree to which an individual feels a lack of control due to chance, fate, luck, or forces he or she does not understand. Our results indicate that it is powerlessness defined as the belief that others are actively controlling one's life which correlates with urinary MHPG levels.

The present findings suggest that there is a link between cognitive processes associated with coping responses and noradrenergic neuronal activity as reflected by urinary MHPG levels. Of interest, in a 17-month follow-up of subjects residing in the area of Three Mile Island, Schaeffer and Baum (28) found an association between the use of positive cognitive reappraisal coping behaviors and lower levels of urinary norepinephrine. Taken together with the results in our current report, these findings suggest the possibility that noradrenergic neuronal activity is related to the cognitive interpretation constructed by the individual to explain environmental events—higher norepinephrine output is associated with perceptions of powerlessness, and lower norepinephrine output is associated with perceptions of mastery. Whether norepinephrine output per se represents a heightened stress response in individuals who construct negative appraisals or whether elevated norepinephrine output detrimentally affects the ability to formulate positive appraisals is not clear and will require further research.

Previous animal studies from our group (12) have demonstrated that the motivational decrements of helplessness as well as a higher rate of release of norepinephrine in the brain may be elicited by neutral environmental stimuli if the neutral stimuli have been paired previously with an uncontrollable stressor. These findings suggest the additional possibility that elevated norepinephrine output may reflect conditioned physiological responses to conditioned environmental stimuli. Recent studies (29) showing higher rates of perceptions of helplessness in depressed women who had experienced the loss of their mothers in childhood support the notion of helplessness as a conditioned response in clinical populations.

Although there is a lack of consensus as to the exact proportion of urinary MHPG that is derived from the CNS as opposed to the periphery (30–32), the evidence remains that urinary measures of catecholamines and their metabolites appear to be useful predictors of both diagnosis and treatment response in depressed patients (16–21, 33–42). Finally, treatment response studies from our group (35–39) and others (40–42) suggest that depressed patients with high urinary MHPG levels are less likely to respond to standard noradrenergically active tricyclic antidepressants such as imipramine, desipramine, and maprotiline than are depressed patients with low urinary MHPG levels. Given our current findings of an association between high urinary MHPG levels and perceptions of powerlessness in patients with unipolar depression, it may be that cognitive-behavioral interventions such as those developed by Beck (43) will prove to be beneficial for these patients.

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# Crack/Cocaine Abusers in the General Hospital: Assessment and Initiation of Care

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*Objective:* Cocaine, either smoked (as "crack") or taken intranasally, is now a common cause of psychiatric illness. This study was designed to assess the impact of cocaine abuse on a general psychiatric service and an obstetrics service in an urban general hospital and to evaluate a program for engaging affected patients in addiction treatment. *Method:* The charts of 300 general psychiatric patients (not admitted for addiction treatment) and 60 cocaine-abusing prenatal or postpartum patients were reviewed. A treatment referral program based on professionally directed peer leadership was established for patients with cocaine abuse. Results of evaluation and referral of 100 other cocaine-abusing psychiatric patients and the 60 prenatal or postpartum patients were then determined. *Results:* Fully 64% (N=191) of the 300 psychiatric patients were diagnosed as substance abusers; 38% (N=113) of them abused cocaine. Almost one-third of these cocaine abusers had no axis I diagnosis other than substance abuse/dependence, and the majority were homeless. Urine samples were positive for cocaine in a majority of the obstetric patients studied. A majority of the psychiatric patients who were referred through the peer-led program enrolled in outpatient cocaine treatment—three times as many as in the chart review group. Most of the obstetric patients suitable for referral enrolled for treatment as well. *Conclusions:* Cocaine abuse may be responsible for a large portion of psychiatric admissions in urban public general hospitals. Cocaine abusers in psychiatric and obstetrics services are apparently responsive to a peer-oriented mode of referral into treatment.

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Abuse of cocaine, whether smoked (as "crack") or taken intranasally, is arguably the most serious psychiatric problem to emerge in the United States in the last decade. Two groups of patients in particular are important to this problem: those admitted to a hospital because of psychiatric sequelae of cocaine addiction and women addicted in the perinatal period. Generally, however, only issues that are immediately related to the hospitalization, such as acute depression or agitation in the former group (1, 2) and delivery and perinatal morbidity in the latter (3, 4), are addressed during a hospital stay. If cocaine-abusing patients are to be drawn into effective outpatient rehabilitation, however, it is necessary to ascertain the nature of this problem in the general hospital and to reorient some parts of the treatment system accordingly. To address this need, we examined an addicted population and developed a model of professionally directed, peer-led intervention for introducing cocaine-abusing patients into long-term treatment. This model drew on both the psychiatric consultation-liaison approach and the drug-free therapeutic community modality for addiction.

## METHOD

The study was carried out at a center-city municipal general hospital in New York that has 1,171 beds, of which 269 are designated for adult general psychiatry and 30 for obstetrics.

On the psychiatry unit, charts of 300 sequentially admitted patients were reviewed with a structured format adapted from the *DSM-III-R* diagnostic criteria for substance abuse and dependence and the Addiction Severity Index (5). Patients admitted to a designated substance abuse treatment service were not included in this

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assessment, as the evaluation was directed only at patients hospitalized for psychiatric indications not having to do with addiction, namely, harmfulness to self or others. A diagnosis of substance abuse or dependence was made from the general psychiatric charts by using the discharge diagnosis assigned by the attending physician or, in the absence of such a diagnosis, the patient's fulfillment of specific *DSM-III-R* criteria on the basis of chart notes indicating relevant signs, symptoms, and history. Characteristics of the following subgroups were then examined in detail: 1) patients who could be diagnosed as abusers of or dependent on either alcohol or any illicit drugs (among these we examined patients who abused cocaine, with or without other drugs) and 2) patients for whom no diagnosis of substance abuse or dependence could be made.

On the obstetrics unit, the clinical staff routinely screened newborns for apparent addiction because of the acknowledged high rate of cocaine abuse among women who gave birth to babies at the hospital. Hospital regulations allow testing of the urine of a newborn for drugs of abuse if addiction is suspected in the mother, and this was generally done when clinically indicated. Using the *DSM-III-R* criteria for abuse or dependence, the obstetrics staff designated a series of 40 postpartum patients for consultation for cocaine problems. Clinical and toxicology findings were assessed as a means of determining the impact of cocaine on patients in the perinatal period. An additional 20 perinatal patients were referred from prenatal and pediatric services for cocaine evaluation.

In the referral program, cocaine-abusing inpatients were approached on both the general psychiatry service and the obstetrics service by a liaison team from the hospital's cocaine treatment clinic to encourage them to accept referral to the clinic after discharge. These patients had been admitted to the hospital after the original chart review. The team, designed to emphasize the peer leadership model in the clinic, consisted of a recovering addict and an addiction counselor who had achieved recovery from drug dependence, supervised by a social worker.

For psychiatric patients, a 27-bed general psychiatric ward was used as the site of the referral program for this study. Staff on this ward were sensitized to the needs of patients with both psychiatric and substance abuse diagnoses through a series of discussion meetings that served to alert them to the benefits of the aftercare program and the role of a peer leadership model in liaison. A twice-weekly discussion group focusing on self-help and addiction aftercare was conducted for cocaine-abusing patients. Patients in the referral program were also brought to visit the cocaine clinic while they were still in their index hospitalization, so as to expose them to their peers and introduce them into the peer-led milieu at the clinic. Records of the hospital's ambulatory psychiatric (and addiction) services were then examined to ascertain which of the patients who had been in the referral program and which of those studied in the chart review had appeared for treatment within 3 months of discharge from the inpatient service.

On the obstetrics service and in the prenatal clinic, patients were contacted by team members and evaluated individually. Postpartum patients were typically referred to the team by the obstetrics social workers if they were suspected of cocaine abuse on clinical assessment or if their newborns' urine was positive for cocaine. The social workers on the obstetrics service generally indicated to these patients that clinic attendance was an alternative to possible placement of the newborn in foster care.

This referral approach was modeled on techniques of peer-led addiction treatment in the general hospital that we had studied previously (6, 7). Patient peers from the cocaine treatment clinic were introduced into both clinical settings, obstetric and psychiatric, with considerable preparation of on-site staff, so as to develop a cooperative working relationship with those responsible for inpatient care. Conferences were held with medical and ancillary staff members to explain the role of cocaine dependence in the presenting pathology, options in effecting referral, and the nature of peer-led treatment. In addition to receiving counseling by the cocaine clinic team, patients were invited to a weekly peer-led meeting at the cocaine clinic, and contact was maintained with patients designated for referral while they were in the hospital.

## RESULTS

The review of charts of 300 patients from the general psychiatric service, all admitted on general psychiatric indications, revealed a high prevalence of addictive disorders, which were associated with severe social disadvantage. Information on the charts showed that 191 (64%) of the patients met criteria for a *DSM-III-R* diagnosis of substance abuse or dependence, most commonly involving alcohol (N=145, 48% of the entire 300), cocaine (N=113, 38%), marijuana (N=50, 17%), and heroin (N=32, 11%). Immediately before hospitalization, more than half of the substance-abusing patients were homeless; that is to say, they were either living in the streets (N=68, 36%) or in municipal shelters (N=32, 17%). The psychiatric illness of these substance abusers also represented a major burden on the health care system, as their mean length of hospital stay was 26.4 days (SD=21.2), and the large majority (N=159, 83%) had previously undergone psychiatric hospitalization. The charts indicated that almost all of these patients had been referred to the hospital's ambulatory psychiatric clinics, but despite this, only 12 (6%) of the patients actually appeared there within 3 months of discharge.

The nature of the cocaine-abusing patients (N=113) within the sample of 300 admissions is illustrated by contrasting them with the patients whose charts revealed no substance abuse whatever (N=109). The cocaine-abusing patients were different on a number of variables, revealing their particular clinical needs beyond their drug use per se. They were significantly younger (mean age=

TABLE 1. Characteristics of Patients Who Abused Cocaine or Who Abused No Substance, Drawn From a Series of 300 General Psychiatric Inpatients

| | Patients Who Abused Cocaine (N=113) | | Patients Who Abused No Substance (N=109) | | Analysis | | |
|---|---|---|---|---|---|---|---|
| Variable | N | % | N | % | $\chi^2$ | df | p |
| Female sex | 25 | 22 | 43 | 39 | 7.83 | 1 | <0.05 |
| Race/ethnicity | | | | | 28.20 | 3 | <0.001 |
| Black | 70 | 62 | 34 | 31 | | | |
| Hispanic | 23 | 20 | 21 | 19 | | | |
| White | 19 | 17 | 50 | 46 | | | |
| Other | 1 | 1 | 4 | 4 | | | |
| Homelessness | 59 | 52 | 33 | 30 | 9.98 | 1 | <0.05 |
| Axis I diagnosis other than substance abuse | | | | | 31.00 | 1 | <0.001 |
| Schizophrenia | 50 | 44 | 63 | 58 | | | |
| Affective disorder | 17 | 15 | 18 | 17 | | | |
| Other psychotic disorder | 6 | 5 | 18 | 17 | | | |
| Other axis I disorder | 4 | 4 | 5 | 5 | | | |
| None | 36 | 32 | 5 | 5 | | | |
| Voluntary admission | 34 | 30 | 19 | 17 | 4.89 | 1 | <0.05 |
| Prior hospitalization | 93 | 82 | 81 | 74 | | | n.s. |
| HIV testing, when available | | | | | | | n.s. |
| Positive | 12 | 11 | 1 | 1 | | | |
| Negative | 10 | 9 | 1 | 1 | | | |

32.9 years, SD=7.9, compared to 41.6 years, SD=7.9; t=5.54, df=168, p<0.001). They were also more likely to be male, black, and homeless, and much more likely to have only a substance abuse diagnosis on axis I (table 1). Furthermore, their average length of stay was somewhat shorter (mean=24.4 days, SD=20.9, compared to 37.7 days, SD=28.6; t=3.94, df=197, p< 0.001). The large majority (N=87, 77%) of the cocaine patients had been given a diagnosis of dependence or abuse by their attending physician; that is, they were generally not undiagnosed. Despite this, only seven (6%) of these patients were referred to the ambulatory psychiatric clinics after discharge and then enrolled.

The clinical staff on the obstetrics ward designate certain postpartum patients as apparent cocaine abusers on the basis of history and clinical findings. A series of 40 women designated in this fashion were evaluated by the liaison team. Urine toxicology screening was done on these mothers and their newborns, and in 24 (60%) of these cases, the urine of one or the other was positive for cocaine. The mean birth weight of the 40 infants was 2810 g (SD=735), and eight (20%) were of low birth weight or "premature" ($\le$2500 g). The majority of these women (N=29, 73%) had previously had children placed in the custody of others, and the majority (N=26, 65%) currently had an open custody case with the city's Child Welfare Administration. Another 20 women were also referred to the cocaine clinic from other hospital sites, primarily from the prenatal clinic (N=12).

In a comparison of the 60 patients from the obstetrics and prenatal clinics and the first 100 psychiatric patients evaluated in the cocaine referral program, the women in the perinatal period were significantly younger (mean age=27.3 years, SD=4.7, compared to 31.3 years, SD=8.5; t=3.73, df=168, p<0.001). The large majority of both groups abused crack cocaine, but the psychiatric patients were more likely than the patients in the perinatal group to have also abused cocaine by the intranasal route and abused other drugs as well (table 2). Although the patients referred from the psychiatric ward were more likely to be homeless, it is notable that very few patients in the perinatal group (N=7, 12%) actually lived in their own homes.

The outcome of the referral program is illustrated in table 2. The majority of the patients referred from both the perinatal group and the psychiatric group to the cocaine clinic enrolled in the cocaine clinic, and five additional patients from the psychiatric group enrolled in the general psychiatric clinics. The mean amount of time between these patients' discharge and their appearance at the clinics was 10.6 days (SD=14). The psychiatric patients were less likely to be referred, however—most commonly because they left the hospital early, against medical advice; others required transfer to long-term facilities or were from remote counties. Altogether, however, more than three times as many cocaine patients in the psychiatric group exposed to the referral program as in the chart-review group eventually enrolled in the ambulatory clinic (22 of 100 versus seven of 113; $\chi^2$=11.3, df=1, p<0.001).

## DISCUSSION

By its very nature, the prevalence of crack/cocaine abuse is hard to measure, particularly among the homeless and indigent. In the Epidemiologic Catchment Area study, for example, a 1-month prevalence of cocaine use of 0% (rounded) was reported (8), but this survey

**TABLE 2. Characteristics of Psychiatric and Obstetric Patients Exposed to a Peer-Led Program to Encourage Treatment for Cocaine Abuse**

| | Psychiatric Patients (N=100) | | Obstetric Patients (N=60) | | Analysis | | |
|---|---|---|---|---|---|---|---|
| Variable | N | % | N | % | $\chi^2$ | df | p |
| Female sex | 19 | 19 | 60 | 100 | 98.40 | 1 | <0.001 |
| Race/ethnicity | | | | | | | n.s. |
| Black | 59 | 59 | 34 | 57 | | | |
| Hispanic | 25 | 25 | 17 | 28 | | | |
| White | 12 | 12 | 7 | 12 | | | |
| Other | 4 | 4 | 2 | 3 | | | |
| Drugs abused | | | | | | | |
| Cocaine, all forms | 100 | 100 | 60 | 100 | | | n.s. |
| Crack cocaine | 66 | 66 | 41 | 68 | | | n.s. |
| Alcohol | 72 | 72 | 29 | 48 | 8.04 | 1 | <0.01 |
| Heroin | 24 | 24 | 3 | 5 | 8.34 | 1 | <0.01 |
| Marijuana | 33 | 33 | 11 | 18 | | | n.s. |
| Homelessness | 45 | 45 | 17 | 28 | 4.79 | 1 | <0.05 |
| Disposition | | | | | 51.20 | 1 | <0.001 |
| Referral to cocaine clinic | 29 | 29 | 50 | 83 | | | |
| Referral to other ambulatory treatment | 5 | 5 | 5 | 8 | | | |
| Further inpatient treatment | 17 | 17 | 1 | 2 | | | |
| Discharge against medical advice | 26 | 26 | 2 | 3 | | | |
| Administrative discharge | 23 | 23 | 2 | 3 | | | |
| Enrollment | | | | | 16.60 | 2 | <0.001 |
| Cocaine clinic | 17 | 17 | 27 | 45 | | | |
| Other psychiatric clinic | 5 | 5 | 0 | 0 | | | |
| Did not enroll | 78 | 78 | 33 | 55 | | | |

was carried out in 1980, before the current "crack epidemic" emerged. The National Household Survey on Drug Abuse reported a 1-month prevalence of cocaine use during 1988 of 1.5% (9), but the White House Office of National Drug Control Policy later estimated that the number of heavy cocaine users was more than twice that reported by this survey (10). Furthermore, the federal Drug Abuse Warning Network tabulates emergency room "mentions" of drugs but cannot describe the full impact of these drugs on patients' health or the cost of attendant pathology in added health services.

Even these figures do little to convey the impact of the cocaine epidemic on the highly disadvantaged and often homeless patients served by public general hospitals, and they do not convey the magnitude of the task that confronts psychiatry in such hospitals in meeting the treatment needs of this population. Reports on drug abuse diagnoses among hospitalized psychiatric patients also often underestimate the problem, since drug abuse may be considered a secondary problem or often go unmentioned, even when it is actually instrumental in the admission. This was first pointed out by Crowley et al. with respect to emergency room admissions (11) and was underlined most recently by Haugland et al. (12), who surveyed directors of general hospital psychiatric services (not addiction services) in New York State on the "dual diagnosis" problem in their facilities. On average, the directors of psychiatric services reported that 31% of their patients were substance abusers, considerably higher than the 15% reported by the state's official database (13).

Our own finding of a prevalence of 38% for cocaine abuse among patients admitted for general psychiatric indications to a center-city public hospital may be more representative of such facilities than is generally appreciated. We found that fully 32% of these cocaine abusers had no other axis I diagnosis, in contrast to the nondrug-abusing psychiatric patients, almost all of whom had axis I diagnoses not associated with substance use. It is unlikely that most of this 32% of cocaine-abusing patients who were admitted (i.e., 12% of all psychiatric admissions) would have required hospitalization in the absence of cocaine use. Furthermore, given the exacerbation of existing psychopathology produced by cocaine (1, 2, 11), it may well be that the current crack/cocaine epidemic precipitated as many as 20% of the general psychiatric admissions to this facility, even though the length of stay was somewhat shorter than that of patients without cocaine abuse. These findings merit replication in a larger, national sample to ascertain true prevalence rates of cocaine-related psychopathology among psychiatric admissions.

Adding further to the burden of the crack/cocaine epidemic on general hospital facilities is the fact that the large majority of the cocaine patients were recidivists and had protracted hospital stays. They were also more likely to be black and homeless than were the patients with single diagnoses and were therefore disadvantaged in terms of available community resources. Furthermore, over one-half of the 20% who were tested for HIV were seropositive, portending a serious risk for transmission, given the reported prevalence of high-risk behavior among these patients (14).

Any assessment of the impact of cocaine in general hospitals must inevitably attend to the issue of perinatal morbidity as well. As Chavkin (3) pointed out, in New

York City 11%–20% of toxicology screens on women in labor in inner-city hospitals are positive for illicit drugs, mostly crack/cocaine; nonetheless, a survey she conducted revealed that the majority of drug treatment programs did not accept pregnant addicts (3). In our hospital as well, urinalyses for a group of 125 women selected at random from those admitted to the obstetrics ward showed 15 (12%) to be positive for cocaine (personal communication from M. Allen). Furthermore, as indicated in our results, the mean birth weight for the babies of the 40 apparent cocaine abusers in our perinatal study group was quite low, a standard deviation below the mean birth weight (3300 g, SD=519) of all live births at the hospital. The rehabilitation problems confronting this population are grave as well, since few of the patients in the perinatal group we evaluated lived in their own homes, and the majority had low-birth-weight babies and were involved in child custody cases.

The task of engaging crack/cocaine patients in addiction rehabilitation is a difficult one, given the very high dropout rates expected from these patients even before treatment is initiated (15). Except for noting dropout as an artifact, however, there has been little attention to this problem in the literature on general hospitals. In our hospital, as in many others, charts generally indicate that a referral was made to the hospital's psychiatric outpatient service, without reflecting the social and communication supports necessary to ensure that patients will appear for treatment. Patients with dual diagnoses, who are likely to be influenced strongly by denial of their addiction, typically ignore the suggested follow-up option unless considerable effort is invested in ensuring an effective referral. Furthermore, 22% of our cocaine abusers were diagnosed in accordance with the *DSM-III-R* criteria upon chart review by the research staff, but they were not given formal diagnoses in the clinical charts by the attending physician. This reflects a further bias against proper referral.

Central to the problem of engagement of these cocaine abusers in aftercare is the absence of a meaningful interpersonal context in which motivation for treatment can be generated while they are in the hospital. Public psychiatric facilities rely heavily on medication for manifest psychiatric symptoms and on the maintenance of a stable, "quiet" milieu. The introduction of enthusiastic support for follow-up care is not common. Addiction problems, because they generally precede and follow hospitalization and are dormant in between, can easily be ignored. The introduction of a peer-led culture infused with the commitment of recovering addicts, on the other hand, can address the issue of the drug problem while patients are in the hospital. It also provides an interpersonal bridge to aftercare, encouraging patients and staff alike to work toward a proper follow-up, which is central to recovery. In order to do this, however, such a program must be sanctioned by clinical leadership and cooperate closely with clinical staff.

In addressing this alternative, we introduced the option of a peer-leadership self-help model into general hospital services. This approach is inherent in Alcoholics Anonymous and related 12-step programs for the addicted. Findings relevant to peer-oriented engagement of patients for treatment of substance abuse have been reported previously. Group treatment modalities have been found useful for patients with dual diagnoses by Kofoed et al. (16) and Hellerstein and Meehan (17); they demonstrate the value of the use of peer support in the treatment process. Galanter et al. (6, 7) found that inpatient alcoholics can be better engaged in ambulatory care by using peer-based self-help from the ambulatory program, and De Leon and Zeigenfuss (18) documented the efficacy of peer leadership in the long-term rehabilitation of drug addicts in therapeutic communities. On this basis we felt that professionally supervised, recovered peer addicts might be a useful device for engaging the crack/cocaine patients on general hospital services.

In evaluating our format for engaging these patients, we considered the appearance of a patient for psychiatric aftercare, at either the cocaine clinic or the general psychiatric clinics, as sufficient. Either setting could provide follow-up after discharge from the hospital. As reported here, our findings therefore evaluated the potential for bringing these seemingly refractory cocaine patients into any appropriate aftercare treatment. They point out the value of using a peer-led referral format as well.

On the psychiatry service, the referral program addressed a majority of the eligible patients and succeeded in increasing threefold the number of patients enrolling in the clinics. This was done by altering the culture on the experimental unit in two ways. The staff was educated to the need for addressing their patients' crack/cocaine problems as well as the acute psychiatric problems that precipitated admission. Furthermore, both patients and staff were exposed to the peer-led culture of the cocaine clinic by introducing recovering addicts into the milieu treatment; the viability of using patient peers as instruments for engagement in aftercare was established, and its favorable outcome was demonstrated.

For the obstetric patients, too, the large majority of those proposed by the ward staff for evaluation were found suitable for referral to the cocaine clinic, and most of them appeared and enrolled in the clinic. Given the high toll of perinatal morbidity associated with cocaine use (4), and the fact that most of these patients were multiparous and likely to become pregnant again, the importance of rehabilitating them cannot be underestimated. This issue is particularly compelling from a medicolegal standpoint, because questions are currently being raised about the imposition of quasi-punitive measures, even criminal charges, on pregnant and postpartum addicts (19).

Crack/cocaine abuse is apparently most common among a highly disadvantaged, often homeless population of predominantly black patients; it certainly is in our hospital. This population is quite different demographically and diagnostically from non-substance-abusing patients. The difference raises the importance of cross-cultural issues in treatment, but these issues often gain limited attention in the mainstream of psychiatric management (20). Nonetheless, these issues go to the core of our conceptions of pathology and treatment. As Rogler (21) pointed out, psychiatric illness cannot be conceived of as a distinct entity concealed by culture but must be understood to be in active interaction with it. Crack/cocaine abuse therefore cannot be viewed as pathology independent of the affected subculture. For example, communication patterns, attitudes toward relating, and networks of acquaintance among our patients were important bases on which the recovering peers were able to engage them for follow-up. These served as a vehicle for establishing supportive ties, one that was not available to the professional staff. Research sensitive to this subculture and its needs must therefore underlie our approach to drug abuse and dependence and the best options for treatment.

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## Commentary

# Homeless Mentally Ill or Mentally Ill Homeless?

Carl I. Cohen, M.D., and Kenneth S. Thompson, M.D.

*Mainstream psychiatry conceptualizes people who are homeless and mentally ill as distinct from other homeless persons because it is thought that their status stems from their mental disorder and the poor implementation of deinstitutionalization. The authors believe this dichotomy is illusory. They present data indicating that recent socioeconomic and political shifts contributed greatly to homelessness among all groups, regardless of mental illness; that those with and without mental illness have similar biographical and demographic profiles; that high levels of mental distress are common to all homeless persons; and that few mentally ill homeless persons require involuntary hospitalization. This perspective suggests novel responses that de-emphasize clinical solutions and focus on empowerment, consumerism, entitlement, community-level interventions, and closer alliances with other advocates for the homeless.*

(Am J Psychiatry 1992; 149:816–823)

> What I wish to do, is to go down into the East End and see things myself. I wish to know how those people are living there, and why they are living there, and what they are living for.
>
> —Jack London (1)

Within psychiatric circles, a debate has emerged between those who use "homeless" as an adjective and "mentally ill" as a noun and those who reverse the order (2, 3). This is not merely a grammatical issue. Rather, as we move into the second decade of mass homelessness, psychiatry faces a critical juncture in its conceptualization of the interplay of homelessness and mental illness.

The most prominent viewpoint within psychiatry has been that the fundamental problem of homeless mentally ill persons is their mental illness. From this perspective, their homelessness is important because it reflects the severity and consequences of their disease. This viewpoint rests on the notions that 1) the occurrence of homelessness among the mentally ill stems primarily from the disabling functional deficits of their disorder (4, 5), and 2) the recent increase in homelessness among the mentally ill is a product of the poor implementation of deinstitutionalization (6, 7). Comments by leaders of the major psychiatric organizations in this country illustrate this viewpoint. In outlining "the perspective of the American Psychiatric Association," Lamb and Talbott (8) wrote, "How do the chronically mentally ill become homeless? . . . The chronically and severely mentally ill are not proficient at coping with the stresses of this world." Similarly, Richard Wyatt (6), chief of the Neuropsychiatry Branch of the National Institute of Mental Health (NIMH), declared, "America's homeless crisis began in 1963 when deinstitutionalization became law through enactment of the Mental Retardation Facilities and Community Mental Health Centers Act. . . . By law, the former residents of structured institutions became the homeless."

On the basis of these perceptions, the problems and service needs of persons who are homeless and mentally ill are conceptualized as being qualitatively different from those of "not mentally ill" homeless persons (9). Like the domiciled severely mentally ill population, the

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homeless mentally ill are viewed as requiring services from an assertive mental health care system capable of satisfying their multiple needs (8). Often, involuntary psychiatric hospitalization is included as a key element of such a system (5, 10, 11). The focus on these specialized needs and services leads to the view that advocacy and program planning for the homeless mentally ill population is best done separately from that for other homeless groups (9).

Our objective is to address this perspective by arguing that, although well-meaning, it is tenuous on empirical and strategic grounds. Underpinning our argument is the notion that the conceptual dichotomy between homeless persons with and without mental illness is largely illusory. On closer examination, "not mentally ill" homeless people have many mental health problems; similarly, the "mentally ill" homeless have numerous nonpsychiatric problems that arise from the sociopolitical elements affecting all homeless people. This alternative perspective, although appearing to be a difference in emphasis, is a conceptual shift. Whereas the mainstream perspective acknowledges that nonpsychiatric factors foster homelessness among the mentally ill, it is believed that mental illness is the "basic, underlying problem" (7) and that other forces impinge on this core deficit. Our model views homelessness as the core element of the broader socioeconomic and political context, which in turn becomes intertwined with personal biography and illness. This alternative perspective perforce spawns novel responses to homelessness and mental illness.

## CAUSES OF HOMELESSNESS AMONG THE MENTALLY ILL

The belief that homelessness is a problem of severe mental illness arose during the early 1980s, when the initial reports about the new homeless appeared in the psychiatric literature (3, 12). Biases were created by methodological weaknesses in the research (13, 14), particularly with respect to the settings in which observations were made (e.g., psychiatric emergency rooms, clinical referrals), and these biases led to inflated estimates—as high as 97%—of the percentage of homeless who were seriously mentally ill (15). In recent years, however, more scientifically rigorous studies sponsored by NIMH have found between one-fourth and one-third of homeless persons to be severely mentally ill (16). Despite the earlier methodological flaws, it is evident that a disproportionate number of homeless persons have severe mental illness.

By dint of their training, psychiatrists have been especially prone to concentrate on individual traits (17). Hence, there has been a tendency to assume that the cognitive and behavioral styles of the mentally ill are the primary causes of their homelessness. Theorists who have focused on these individual characteristics of mentally ill homeless persons point to their propensity to "drift," to "wander," to "outrun problems," to be "disorganized," to have "poor problem-solving abilities," and to be unable to "deal with even ordinary landlord-tenant situations" (4, 5, 8, 10). Nevertheless, none of these reports has been able to demonstrate how mental illness alone causes homelessness (18).

A corollary of the belief that the disabilities of severe mental illness lead to homelessness is the conviction that mental health services should enable patients to overcome their disabilities and thereby allow them to be domiciled in the community. From this perspective, the increase in the occurrence of homelessness among the mentally ill is taken as evidence of the failure of community-based services and the policy of deinstitutionalization (6, 7, 9, 15, 19). However, it is unlikely that the current practice of deinstitutionalization and community-based care is the primary reason for homelessness among the severely mentally ill. First, it should be underscored that of the 2 million schizophrenic persons in the country, fewer than 8% are living in public shelters or on the streets (20). Nearly one-half live with their families. Moreover, given the high volume of discharges from psychiatric institutions and the increased restrictions in hospital admission policies during the 1960s and early 1970s, it might have been anticipated that large numbers of mentally ill persons would have become homeless during this period if the primary cause of homelessness was the shift in patient care from institutions to inadequate community-based mental health services. Yet evidence points to a significant temporal gap: the dramatic increase in homelessness among the mentally ill occurred only at the very end of the 1970s.

Several writers have noted that the policy of deinstitutionalization also affects increasing numbers of "new" chronic mentally ill individuals, who in years past would have been long-term residents of state hospitals and who are now further expanding the homeless mentally ill population (3, 12). Implied in this framework is the assumption that many of the new chronic mentally ill homeless require institutionalization (21); however, as we will discuss, the data suggest otherwise. Fisher and Breakey (22) concluded after a comprehensive review of the literature that, although deinstitutionalization is often blamed for the increase in homelessness, "empirical data to support this view are sparse" (p. 20), a view shared by Tessler and Dennis in their review of NIMH-sponsored research on homeless mentally ill persons (23). Even if deinstitutionalization had been better implemented, other, more dominant social forces would have likely continued to spawn more homelessness among the mentally ill.

The past 15 years have been characterized by marked social, political, and economic changes, which are much more likely to have contributed to the dramatic increase in homelessness in general, as well as among those with mental illness. For example, there has been a rapid decline in the availability of low-cost housing. Wright and Lam (24) observed that at this stage of American history there is simply not sufficient low-income housing to accommodate the poor population; consequently, "the new homeless are largely victims of a housing market that is assuredly not of their own making." Data suggest that most homeless mentally ill persons lost their rooms in single-room-occupancy hotels or low-priced apartments not because of psychoticism but because they 1) were evicted because of renewal projects and fires, 2) were victimized by unscrupulous landlords or by other residents, or 3) could no longer afford the rent (25). For example, in New York City, during 1975–1981 more than 30,000 rooms in single-room-occupancy residences were lost; 10,000 such rooms were lost in San Francisco during the 1970s (26). The experience of one of us (C.I.C.) as a community psychiatrist working in midtown Manhattan is similar to the experiences of others in the field. During the mid-1970s, it was unusual to encounter difficulty placing discharged patients in single-room-occupancy hotels. By the early 1980s, however, hotel managers not only refused to accept new tenants with psychiatric histories but often refused to reaccept old tenants who had been hospitalized. Ironically, in these instances, institutionalization, rather than deinstitutionalization, contributed to homelessness.

Other major socioeconomic dislocations that have occurred in the last 15 years include the loss of many manufacturing jobs, which have been replaced, if at all, by low-wage service positions (27), and the Reagan administration's targeting of social welfare programs, which led to the elimination or reduction (actual or secondary to inflation) of social welfare benefits (26). It is important to note that these dislocations and their effects were not randomly distributed throughout the population. Rather, during the 1980s poor and marginal populations suffered further deprivation (28). As a result, the nature, form, and distribution of poverty in the United States has shifted substantially in the last 20 years (18, 26, 27, 29–35). The upsurge in homelessness is one example of these changes and may be best seen as the most extreme form of this new destitution (18, 26, 33, 36, 37). As might be expected, people of color have been differentially affected by these socioeconomic processes. For example, the percentage of poor African-Americans living in extremely poor neighborhoods increased from 25% to 40% during the 1980s (38). Changes of this kind account for the disproportionately high numbers of African-Americans and Latinos among the homeless, a finding that has been documented in numerous studies (23, 33).

Persons with severe and persistent mental illness have been excessively burdened by these dislocations because of their symptoms, disabilities, lack of resources, dependence on others, and susceptibility to stigma, neglect, and victimization (39). This vulnerability has been compounded as the historical safety net for at-risk individuals provided by families and community supports has been torn asunder by the weight of poverty and its associated pathologies, such as drug use, crime, violence, and disease. Consequently, the population of severely mentally ill living in the community has been swept along with other relatively powerless and vulnerable populations, such as poor African-Americans, into increasing poverty, resourcelessness, and homelessness, to become a part of a destitute population referred to by some as the "underclass" (27, 40).

These processes recall longstanding historical forces in industrial society. For example, Foucault noted that in seventeenth-century France such forces "seemed to assign the same homeland to the poor, to the unemployed prisoners, and to the insane" (41). Thus, along with other homeless groups, the homeless mentally ill must first be seen as impoverished and disenfranchised, rather than diseased. From this perspective, the policy of deinstitutionalization is important because once mentally ill persons are released into the community, they are exposed to these detrimental forces. Many homeless persons with mental illness also see things this way. In a study conducted in Ohio (42), homeless mentally ill people identified their economic and social problems, rather than symptoms of mental illness, as the principal reasons for their homelessness.

## COMMONALITIES WITH OTHER HOMELESS PERSONS

In light of the findings just described, the position that persons who are homeless and mentally ill are a unique subgroup becomes more questionable. Just as the principal causes of homelessness do not differentiate the mentally ill homeless from the homeless who are not mentally ill, research comparing them has shown little difference in their demographic profiles, geographic origins, work skills, and levels of substance abuse; the extent to which family or economic problems contributed to their homelessness; and the size of their social networks (23, 43, 44). For example, in a study by one of us (C.I.C.) (44), according to relatively sophisticated network measures, only one-seventh of each group reported two or fewer network links and no subject was a total isolate. Thus, the stereotype in the psychiatric literature of the lone psychotic person huddling in a doorway may be the exception rather than the norm.

Noteworthy in this regard are the findings of Foulks et al. (45) for homeless chronic mentally ill veterans, who did not differ from the general population in their performance on neuropsychological tests and exhibited particular cognitive strengths in planning and foresight. Furthermore, work by Anthony et al. (46) has debunked the notion that there is a strong correlation between a person's psychiatric symptoms and a person's skills. Indeed, the fact that many homeless persons with chronic mental illness successfully survive on the streets and in shelters belies the notion that these individuals are unable to cope with life stresses. Psychiatrists serving the homeless mentally ill may be susceptible to the "clinician's illusion" (47), i.e., the belief that persons with more longstanding and more pronounced disorders are more likely to show up in clinical caseloads. As a consequence, psychiatrists are prone to view the "mentally ill" homeless as more numerous and markedly disabled and to underestimate or ignore mental distress among the rest of the homeless population.

The severely mentally ill and "not mentally ill" share the extreme stress of the experience of homelessness. The initiation into homelessness is a crisis (48) that results from a concatenation of many life crises and stressors. Once a person has become homeless, the stressors escalate. One homeless man lamented, "I can't relax my body, lay down, and sleep. It's no joke sitting up in a hard bench sleepin'. Every time somebody passes and scrapes their feet, you jump up. My nerves is on edge 'cause I've seen people attacked in the park. I was sitting in Central Park, day was just breaking, and a guy picked up a wire basket and beat another man to death" (44, p. 94).

A psychiatry resident at the Uniformed Services College of Medicine related that he was granted permission to do an elective in the Washington, D.C., shelters on the grounds that it was the closest approximation to combat conditions that existed in peacetime (R. Koshes, personal communication).

It is axiomatic that homelessness is accompanied by feelings of disconnectedness, self-blame, demoralization, and powerlessness, regardless of the presence or absence of a severe and persistent mental illness. In fact, unless the term "mental illness" is limited to the major psychotic and affective disorders on axis I of *DSM-III-R*, it is difficult to segregate a subpopulation of the homeless mentally ill from the general homeless population. Several studies have shown high rates of substantial depressive symptoms among the homeless (33, 48, 49, 50). For example, in Rossi's study in Chicago (33), demoralization was rampant and nearly one-half of the subjects had depressive symptoms felt to be severe enough to warrant treatment. In a study of older homeless men (44) conducted by one of us (C.I.C.), one-fourth of the subjects said they wished they were dead. In a similar vein, the prevalence of alcohol and substance abuse and dependency among the homeless is also known to be extremely high (23, 51). It is clear from these studies that emotional distress and behavioral problems are essentially ubiquitous among the homeless. Finally, it would be disingenuous to contend that no differences exist between the mentally disabled and not mentally disabled homeless populations. For example, in a review of NIMH-funded studies, Tessler and Dennis observed that "compared to non-impaired homeless individuals, mentally disabled homeless persons were more likely to be homeless for longer periods of time, to have less contact with families and friends, to have more barriers to employment, poorer physical health, and more contact with the legal system" (23, p. 36). Nevertheless, although these differences are not unimportant, the cumulative evidence we have outlined weighs heavily in favor of the commonalities, rather than differences, as the primary determinants of homelessness.

## SERVICE APPROACHES

Mainstream psychiatry's relatively recent recognition that homeless persons with psychiatric problems may benefit from assertive, comprehensive, and coordinated psychiatric and social welfare services is commendable. Nevertheless, it is frequently reported that the mentally ill homeless refuse these services. Before we conclude that their resistance to these services arises from their disordered thinking, we must first examine the manner in which services are offered. Although well-intentioned, psychiatry has tended to focus primarily on the psychiatric deficits of homeless people to the relative exclusion of their shared social environments, their individual and collective strengths, and their essential rights and privileges as citizens. As a result, the strategy used has been paternalistic (or maternalistic) rather than focused on context, entitlement, and empowerment (52). The former approach frequently engenders feelings of humiliation, although this is not fully appreciated by most service providers. As Orwell observed nearly 60 years ago, "A man receiving charity practically always hates his benefactor—it is a fixed characteristic of human nature" (53). Because psychiatry has focused almost exclusively on pathology, there is a lack of understanding of the living conditions and life attitudes of people occupying the margins of society, leading to substantial miscommunication and misunderstandings between service providers and the served (54).

The problems of disempowerment and stigma are also exacerbated by psychiatry's concentration on disease and its subsequent emphasis on directing mental health services to those whose conditions meet certain criteria for chronic mental illness. This creates problems because many homeless emotionally distressed or disabled people, chronically mentally ill or not, do not view themselves as mentally ill (3), and some have had previous negative experiences with mental health care systems. For example, a consumer-oriented survey by Goering et al. (55) indicated that part of the reason for the presumed resistance to accepting services was an incongruence between the client's priorities and the mental health services offered. Many of the homeless mentally ill persons surveyed felt disenfranchised and exhibited considerable antipathy toward any formal system. Like most people, the homeless mentally ill generally desired a safe, comfortable home and did not wish to be segregated in residences for the mentally ill, which they perceived as dangerous and stigmatizing. Hence, the form and content of disease-focused services as presently constituted often reflect insensitivity to the desires, experiences, and social world of homeless people in psychiatric distress—a point that has sometimes been missed by those (e.g., the APA Task Force on the Homeless Mentally Ill) who have viewed these individuals as primarily a subgroup of the chronic mentally ill.

The failure of current approaches to engage the homeless mentally ill in services and get them off the streets has led to a mounting call by some for their involuntary hospitalization (4, 10). Embedded in this demand is a belief that civil libertarians have created a situation in which the homeless mentally ill have become too entitled and are protected by stringent commitment laws that allow them to follow their own wishes and, as a result, permit them to perish in the streets with "their rights on" (56, 57).

Although we concur with the notion that mentally ill homeless persons who are incompetent to make decisions about accepting treatment, who are dangerous to themselves or others, or who are gravely disabled should be hospitalized against their wills (4, 5, 10), in actuality few mentally ill homeless persons meet these criteria unless the criteria are stretched beyond their intended meanings and thereby threaten the protection of human rights. In fact, an examination of data from Project Help in New York City—which is often cited as a model program for involuntary hospitalization (4) because of its broader definitions of dangerousness to self or others—reveals that roughly two-thirds of the homeless persons targeted for hospitalization by Project Help were ultimately deemed unqualified for involuntary hospitalization (58). Comments by staff of Project Help are revealing: "Many of the homeless are overtly psychotic, yet have adapted to the life in the streets and are not at significant risk" (59, p. 924). Similarly, Snow et al. found that "efforts of the homeless mentally ill to survive on the streets are not as chaotic or as irrational as they appear from a distance" (60, p. 418). Several well-designed studies (61–63) have supported these observations, showing that only 5%–7% of single adult homeless persons are in need of acute inpatient care.

Yet there is a grain of truth in the observation that being entitled to stay out of institutions is a real problem for the homeless mentally ill and society. However, unlike those who focus first on mental illness and believe that the homeless mentally ill have too many rights, our focus on homelessness reveals that the mentally ill homeless, like the rest of the homeless, do not have enough rights. Their right to be truly in the community is merely theoretical until they have procured the legal, political, therapeutic, and economic means necessary to construct and maintain a secure niche within the community.

Emphasizing homelessness challenges the current scope and nature of psychiatric concern and practice with homeless populations. It calls for the profession, along with others, to cast a wider net so as to recognize and address the broad social and psychiatric causes and effects of homelessness and destitution, helping the homeless to solve their problems and to build a new, more humane niche for themselves in society. Among other things, this necessitates a restructuring of clinical encounters with patients so that they are less paternalistic and disease oriented and are more focused on empowering individuals and groups to solve their problems by eliciting sources of health and strength (64–67). This perspective recognizes that individual-oriented clinical and social services are not sufficient in themselves. Rather, they must be integrated with a range of social psychiatric interventions that are akin to the strategies used with refugees, displaced persons, and persons experiencing extreme life stressors, such as combat veterans, cancer survivors, and disaster victims. Thus, in addition to clinical attention on the individual level, this entails the kinds of systems-level interventions advocated by mental health professionals in communities that have endured major catastrophes (68) or other forms of social instability (69). Examples of this work are 1) the establishment of settings that provide permanent independent living with ongoing social supports and 2) an effort by one of us (K.S.T.) and others to establish a therapeutic community in a men's shelter. On a much larger scale, an example of this kind of approach can be found in the report "To Build a Community," produced by the Los Angeles Citizens' Task Force on Central City East, an area of Los Angeles where the homeless congregate (70). In addition to traditional community mental health services, the report called for large-scale preventive projects to identify at-risk individuals, community development programs including conflict management and consensus building, and close collaboration with universities to develop model service programs.

## ADVOCACY

It is doubtful whether separately advocating on behalf of the mentally ill homeless, as opposed to the homeless and destitute in general, makes sense from either a pragmatic or moral perspective. In recent years psychiatrists have become more biomedically focused and have been circumspect about addressing broader sociopolitical issues, which are thought to be outside their purview (71). Although social and political contexts have been recognized, they have not been well integrated into etiological theory. However, several analysts (31, 72–74) have noted how "medicalizing" social conditions such as homelessness tends to deflect solutions away from the social arena and onto individuals. Similarly, we have seen in other disciplines that theorizing which is not based on context can have pernicious consequences (e.g., explanations of lower IQs among African-Americans) (75). It is noteworthy that the 320-page APA task force report on homelessness (12) devoted merely two sentences and no analysis to the disparity between the numbers of homeless people of color and homeless whites. It has remained for other social scientists to examine the links between racism, poverty, and homelessness.

We have shown why psychiatry must extend its theoretical and clinical gaze beyond the chronic mentally ill homeless population, not to forget them but to include them with others in the community and to make certain that it does not neglect persons suffering from nonchronic forms of mental distress (18). Psychiatrists must collaborate with other social scientists and human service workers in confronting social problems, particularly poverty and destitution, and their effects on individuals, families, and communities. This means that psychiatry must give greater priority to examining the connections between public issues and private troubles, a part of the process aptly named "the sociological imagination" by C. Wright Mills (76). This is particularly important for public psychiatry, which, by concentrating on deinstitutionalization, chronicity, and the disease paradigm, has minimized its obligation to provide a full range of psychiatric services to the poor in need, regardless of chronicity (77).

The separation of the homeless mentally ill from the homeless in general creates a false division, pitting what many might see as the morally deserving homeless who are mentally ill, not at fault, and therefore worthy of public largesse against the unworthy, nondeserving homeless underclass who are destitute by choice, not illness. Besides being unscientific, such a morally tinged subdivision of the homeless may backfire on both the severely mentally ill and the objectives of the profession. Are the homeless mentally ill any more deserving than the children, women, elderly, veterans, or unemployed men who are homeless? In addition, historically it has been difficult to persuade legislatures to fund large-scale programs for chronic mentally ill individuals, even when the mentally ill are domiciled and successful models exist (78). How likely are legislatures to support the development of what amounts to a special (and extremely expensive) social welfare and treatment system for the chronic mentally ill alone? Scull (79) described this dilemma as it occurred historically in Britain:

> To improve the living conditions of lunatics living in the community would have entailed supplying relatively generous pension or welfare benefits to provide for their support, implying that the living standards of families with an insane member would have been raised above those of the working class generally . . . something approximating a modern social welfare system, while their brethren were subject to the rigours of a poor law based on principles of less eligibility.

Finally, mental health workers must recognize the primacy of homelessness in order to ally themselves with other advocates for the homeless and destitute, including the homeless themselves. In this way, the overriding social and political etiological factors may begin to be addressed. By working in concert to develop meaningful social solutions (including better mental health services), all vulnerable subgroups, including the chronically mentally ill, will benefit. Prospects for social change are made more likely by increasing discontent, particularly among the one-third of the nation's families who are now "shelter poor" (i.e., unable to pay for nonhousing necessities and still cover housing costs) and among urban dwellers, such as those in New York, where one in nine persons live in imminent danger of homelessness or at high risk for future homelessness, by the homeless themselves as they begin to organize politically, and by the rising tide of concern for social responsibility with the end of the Cold War and the Reagan era (80–82). Thus, one can envision a future alliance between the homeless, the working class, and other socially concerned persons, including professionals, in support of new initiatives that would include governmental housing programs, improved health services, rejuvenated antipoverty programs, and community development projects.

Although empirical evidence and the limited progress made in the past decade in addressing the problems of mental illness among the homeless bespeak a revision of prevailing theory and strategies along the lines outlined in this paper, American psychiatry has not appreciably altered its position since the original APA report in 1984. In 1990 the APA Task Force on the Homeless Mentally Ill issued an interim report (83) that stated, "The comprehensive [sic] view of the initial APA recommendations remains an excellent embodiment of principle." Ironically, the original decision to separate the chronic mentally ill from other homeless populations was never made on empirical grounds; rather, it was based on an a priori belief that the task force's credibility would be enhanced (8). More encouraging has been the task force's recent report on homeless families and children (84), which, in contradistinction to its position on single homeless persons, is more encompassing and less clinical in that it includes all families, regardless of degree of mental illness. Such broad-based approaches are necessary because past experience has amply demonstrated that major advances in services for the mentally ill—notably following World War II and in the 1960s—have come primarily through alliances in which mental health services are conceptualized as one component of a wide-ranging social agenda (85, 86).

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# Are Panic Attacks Traumatic Stressors?

Richard J. McNally, Ph.D., and Brian M. Lukach, M.S.

*Like typical stressors that produce posttraumatic stress disorder (PTSD), panic attacks are sudden, unpredictable, and often perceived as life-threatening. Structured interviews with 30 subjects with panic disorder revealed that five (17%) and two (7%) met lifetime and current* DSM-III-R *PTSD criteria, respectively, following their most terrifying panic attack. PTSD produced by panic is less severe than PTSD produced by either rape or combat.*

(Am J Psychiatry 1992; 149:824–826)

A characteristic cause of posttraumatic stress disorder (PTSD) is exposure to a sudden, unpredictable, life-threatening event, such as gunfire or violent rape. Although the individual may emerge physically unscathed from the trauma, the perception of a close brush with death is often sufficient to trigger the syndrome (1). Indeed, most studies have uncovered a dose-response effect whereby the severity of PTSD symptoms varies as a function of perceived threat (2, 3). Although perceived threat is usually highly correlated with actual threat, theorists have speculated whether perceived threat alone may suffice to produce PTSD (unpublished 1989 paper of J.S. March).

Spontaneous panic attacks are sudden, unpredictable events that are commonly perceived as life-threatening. Indeed, according to some cognitive theorists (4), panic cannot occur unless the individual believes he or she is in imminent danger (e.g., of dying from a heart attack). If the perception of danger is necessary for panic to occur, and if such perceptions are sufficient to produce PTSD, persons with panic disorder should ordinarily develop PTSD.

To test whether panic constitutes a traumatic stressor, we assessed the occurrence of PTSD symptoms in subjects with panic disorder and compared their pattern of symptom endorsement with that of a comparison group of subjects with PTSD.

## METHOD

The group of subjects with panic disorder comprised 25 women and five men with the disorder. We used the Structured Clinical Interview for DSM-III-R (SCID) (5) to establish the diagnosis. Subjects ranged in age from 17 to 47 years (mean=33.5), and their number of years of education ranged from 10 to 19 (mean=13.3). They were recruited from the anxiety disorders clinic of an urban medical school, an agoraphobia treatment center in a suburban area, and a support group in a suburban area. All were unpaid, and all volunteered when asked to participate in an interview study concerning panic. Clinic patients were consecutively referred patients who sought behavioral treatment for panic disorder; the remaining subjects with panic disorder were randomly selected from among active support group members.

The group of comparison subjects comprised 17 male Vietnam veterans with combat-related PTSD who were inpatients on a Veterans Administration stress disorder treatment unit and one male and 12 female community volunteers with rape-related PTSD. The diagnosis of PTSD was established by SCID interviews in two unrelated studies in which these subjects participated. The comparison subjects ranged in age from 22 to 53 years (mean=37.6), and their number of years of education ranged from 9 to 18 (mean=14).

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To assess the occurrence of PTSD symptoms in the subjects with panic disorder, we used the SCID PTSD module developed by Kulka et al., in collaboration with Spitzer et al., for the Vietnam Veterans Readjustment Study (6). After ruling out a history of *DSM-III-R* traumatic stressors that might produce PTSD symptoms, we asked subjects with panic disorder to identify "the most frightening panic attack you ever experienced, perhaps one in which you thought you were about to die." Once they specified an attack, we asked them to estimate, in percents (1%–100%), the likelihood that they thought they were about to die during the attack. Using the SCID, we assessed the occurrence of PTSD symptoms in reference to this attack. Subjects then completed the Impact of Event Scale—Revised (7) in reference to their most frightening panic attack. Their scores were compared with those of the 12 subjects with rape-related PTSD for whom we had Impact of Event Scale—Revised data.

## RESULTS

According to their scores on the SCID, five (17%) of the 30 subjects with panic disorder qualified for a lifetime diagnosis of PTSD, and two (7%) qualified for a current diagnosis of PTSD. The mean subjective rating of the likelihood of impending death during the worst panic attack by the five subjects with panic disorder who also had PTSD was 72% (range=0%–100%); the rating by the 25 subjects with panic disorder who did not have PTSD was 56% (range=0%–100%) ($t<1$, df=28, n.s.).

Chi-square tests (Yates-corrected) indicated that a higher percentage of the 30 subjects with PTSD than of the five subjects with panic disorder and a lifetime diagnosis of PTSD endorsed each of the 17 PTSD symptoms on the SCID except for the startle response. A significantly higher percentage of subjects with PTSD than of subjects with panic disorder and PTSD endorsed nightmares, flashbacks, psychogenic amnesia, loss of interest, concentration problems, and physiological reactivity to reminders of the trauma (table 1).

Two-tailed t tests indicated that the 12 subjects with rape-related PTSD for whom Impact of Event Scale—Revised scores were available had a significantly higher mean total score on this scale than the 30 subjects with panic disorder (46.3, SD=7.1, versus 33.0, SD=15.4) ($t=3.81$, df=39, $p<0.001$), as well as a higher mean avoidance subscale score (21.9, SD=3.0, versus 17.9, SD=9.0) ($t=2.15$, df=39, $p<0.05$) and higher mean intrusion subscale score (24.2, SD=7.2, versus 14.9, SD=8.2) ($t=3.43$, df=40, $p<0.001$). Two-tailed t tests indicated that the 12 subjects with rape-related PTSD did not have a significantly higher (p values greater than 0.10) mean total score (41.8, SD=6.6), avoidance subscale score (21.8, SD=4.6), or intrusion subscale score (20.0, SD=4.0) on the Impact of Event Scale—Revised than the five subjects with panic disorder and PTSD. Thus, the Impact of Event Scale—Revised was sensitive to the presence of PTSD as diagnosed by the SCID.

**TABLE 1. *DSM-III-R* PTSD Symptoms Endorsed by Subjects With PTSD, Panic Disorder, and Panic Disorder With PTSD**

| | Subjects With PTSD (N=30) | | Subjects With Panic Disorder (N=30)[a] | | Subjects With Panic Disorder and PTSD (N=5) | |
|---|---|---|---|---|---|---|
| Symptom | N | % | N | % | N | % |
| Intrusive thoughts | 30 | 100 | 10 | 33 | 4 | 80 |
| Nightmares[b] | 28 | 93 | 3 | 10 | 1 | 20 |
| Flashbacks[b] | 27 | 90 | 0 | 0 | 0 | 0 |
| Psychological distress | 28 | 93 | 11 | 37 | 4 | 80 |
| Avoid thinking or feeling | 28 | 93 | 10 | 33 | 4 | 80 |
| Avoid reminders | 23 | 77 | 5 | 17 | 3 | 60 |
| Psychogenic amnesia[b] | 18 | 60 | 0 | 0 | 0 | 0 |
| Loss of interest[b] | 26 | 87 | 2 | 7 | 1 | 20 |
| Cut off from others | 26 | 87 | 9 | 30 | 4 | 80 |
| Numbness | 26 | 87 | 2 | 7 | 2 | 40 |
| Foreshortened future | 27 | 90 | 10 | 33 | 5 | 100 |
| Sleep problems | 29 | 97 | 8 | 27 | 3 | 60 |
| Irritability | 25 | 83 | 12 | 40 | 3 | 60 |
| Concentration problems[b] | 26 | 87 | 7 | 23 | 1 | 20 |
| Hypervigilance | 29 | 97 | 17 | 57 | 4 | 80 |
| Startle response | 29 | 97 | 15 | 50 | 5 | 100 |
| Physiological reactivity to reminders of the trauma[b] | 28 | 93 | 6 | 20 | 2 | 40 |

[a] The panic disorder group includes the five subjects who qualified for a lifetime PTSD diagnosis.

[b] These PTSD symptoms were endorsed more frequently by the PTSD group than by subjects with panic disorder who also qualified for a lifetime diagnosis of PTSD ($p<0.05$).

## DISCUSSION

Although panic attacks are sudden, unpredictable events that are often perceived as life-threatening, they produce PTSD far less often than prototypical traumatic stressors (e.g., exposure to gunfire) (2). Certain characteristics of panic may diminish its traumatogenic potential. For example, panic attacks are often misperceived as heart attacks, and heart attacks are more common and more in the range of everyday experience than prototypical traumatic stressors. On the other hand, heart attacks rarely strike young people, and young people are those most at risk for panic disorder. For them, heart attacks are outside the range of everyday experience.

Perhaps the "internal" locus of panic renders it less traumatogenic than prototypical "external" traumatic stressors. The findings of two studies (8, 9), however, suggest that internal stressors may produce PTSD. As many as 25% of patients who survived a myocardial infarction (8) and as many as 46% of those who recovered from a psychotic episode (9) experienced PTSD. However, in neither study did the investigators use structured diagnostic interviews or rule out a history of exposure to prototypical external trauma. Moreover, in the latter study (9), the phenomena that postpsychotic patients reported reexperiencing primarily concerned "external" events surrounding involuntary hospitalization (e.g., forced sedation) rather than "internal" psychotic symptoms per se (e.g., frightening hallucinations). Nevertheless, these findings suggest that structured interviews to assess the occurrence of PTSD are warranted, especially in heart attack survivors.

Most plausibly, subjects with panic disorder may entertain multiple, shifting interpretations of their symptoms during a panic attack. That is, they may fear that they are having a heart attack without being convinced of it. In contrast, most external traumatic stressors (e.g., exposure to gunfire) do not leave room for such varied and potentially noncatastrophic interpretations. Thus, the inherent ambiguity of panic may attenuate its traumatogenic potential.

In summary, this study has etiological implications for both PTSD and panic disorder. Our findings are consistent with the view that an objective definition of what constitutes a traumatic stressor ought to be retained in the *DSM-IV* criteria for PTSD. That is, threats may need to be actual as well as perceived for PTSD to occur. On the other hand, our findings also suggest that catastrophic thoughts may not necessarily precede even the worst panic attacks of those with panic disorder (10). That is, even during their most frightening attack, patients may not be wholly convinced that danger is truly imminent.

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# Onset of Panic Disorder

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*The situations in which the first panic attack occurred were investigated in 44 patients affected by panic disorder. Although the first panic attack was reported to be unexpected and no avoidance was present before it, 75.8% of patients (N=22) with panic disorder with agoraphobia had their first panic attack in phobogenic situations, compared with 20% of patients (N=3) with panic disorder without agoraphobia.*

(Am J Psychiatry 1992; 149:827–828)

Since the introduction of panic disorder as a separate nosological category there has been considerable debate on this subject. On one hand, a position, which is usually referred to as the "American view," maintains that spontaneous panic attacks constitute the core of the disorder, phobic avoidance being secondary to the recurrences of panic attacks. On the other hand, the so-called "European view" contends that phobic attitudes may exist before the occurrence of panic and that this peculiar cognitive style is the primary aspect of the illness. Although the issue can be solved only by prospective studies, the observation of the context in which the first panic attack occurs may offer a different angle for exploring the problem. Lelliott et al. (1) reported that 92% of their agoraphobic patients with panic experienced their first panic attack in public places rather than at home.

Because these findings merit further consideration and, to our knowledge, no other study has replicated them, we decided to explore in detail the circumstances of the onset of panic disorder. Since we had the opportunity of being referred a certain number of subjects during the initial stages of their illness, we explored only those cases in which the first panic attack had occurred shortly before the interview (within 6 months) in order to improve the reliability of recall. Using an approach different from that of Lelliott et al. (1), who studied only agoraphobic patients with panic disorder, we investigated patients with panic disorder, whether with agoraphobia or not.

## METHOD

Of the patients referred to our outpatient facility during 1988–1989, 98 satisfied *DSM-III-R* criteria for panic disorder, and in 44 of these the onset of the illness was precisely datable to within 6 months of the interview. Of these, 15 patients had no sign of phobic avoidance and 29 were agoraphobic (five at a mild level, 10 at a moderate level, and 14 to a severe degree). Patients with panic disorder with and without agoraphobia did not differ in sex (female:male ratio=18:11 for phobic and 9:6 for nonphobic patients), age (mean=25.1 years, SD=5.8, versus mean=24.1, SD=5.1), or education (mean=11.9 years, SD=5.3, versus mean=10.8, SD=5.1).

The symptoms of and the circumstances when the disorder occurred the first time were investigated in detail by a specially devised structured interview. The presence of agoraphobia before the first panic attack was investigated by a self-rated inventory that evaluates the distress experienced in 16 typical agoraphobogenic situations on 7-point rating scales. The patients' past personal history was evaluated by the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (2) in order to exclude patients with previous forms of anxiety disorder.

## RESULTS

In all the patients the disorder began with an unexpected panic attack, and, in the patients in whom agoraphobia was present, it developed later, after a time lag varying from a few days to a few weeks after the first panic attack. None of the patients reported any form of distress when exposed to phobogenic situations before the onset of panic disorder. Development of phobias was unrelated to the number of unexpected panic attacks.

The situations in which the first panic attacks occurred are listed in table 1. The first panic attack occurred in "places or situations from which escape might be difficult (or embarrassing) or in which help might not be available" (*DSM-III-R*) in 22 (75.8%) of the 29 patients with agoraphobia compared to three (20%) of the 15 patients with panic without agoraphobia ($\chi^2$=12.57, df=1, p<0.001). Using the distinction of Lelliott et al. (1) between public and nonpublic places did not change the results to an appreciable extent.

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**TABLE 1. Places and Situations Where the First Panic Attack Occurred for 44 Patients With Panic Disorder in Florence, Italy**

| | Panic Disorder | |
|---|---|---|
| Place and Situation | With Agoraphobia | Without Agoraphobia |
| City bus alone | 3 | 1 |
| Highway | | |
| Driving alone | 6 | 0 |
| Driving with family | 0 | 1 |
| Crowded place | | |
| Discothèque with friends | 1 | 0 |
| Church alone | 2 | 0 |
| Restaurant with colleagues | 2 | 0 |
| Supermarket alone | 1 | 0 |
| Hairdresser alone | 1 | 0 |
| Stadium with child | 1 | 0 |
| City center alone[a] | 2 | 0 |
| In another city | | |
| Alone | 3 | 0 |
| With friends | 1 | 0 |
| Walking on a bridge alone | 1 | 0 |
| Attending class | 1 | 1 |
| Military draft examination | 1 | 0 |
| At computer at work | 0 | 2 |
| Home | | |
| Sleeping | 0 | 2 |
| Alone | 1 | 1 |
| With family | 2 | 7 |

[a] Downtown Florence is usually crowded with tourists.

## CONCLUSIONS

Where we found that most agoraphobic patients experienced their first panic attack in phobogenic situations, our findings are consistent with those reported by Lelliott et al. (1). In addition, we found that such an onset was significantly less common among patients with panic disorder who did not develop agoraphobia.

However, there are some inconsistencies between our findings and those of Lelliott et al. First, none of our patients reported any clinically evident form of distress when in phobogenic situations before the onset of panic disorder. This also contradicts the report of Fava et al. (3) of patients with panic disorder having phobic symptoms before the onset of panic. Second, the first attack was totally unexpected, and the patients' feeling of being entrapped developed along with the surging of panic and not before the attack. We believe that the different ways of recruiting the patient groups could have accounted for such discrepancies: patients with unselected panic disorder at the initial stage of their illness in our study and patients suffering from panic disorder with agoraphobia who were referred for cognitive/behavior therapy in the studies of Lelliott et al. and Fava et al.

Our results might be biased by the fact that a certain proportion of patients without agoraphobia could become agoraphobic after the 6-month observation period. However, when the data were analyzed, almost all the patients had been followed up for at least 2 years, and none of those without agoraphobia had developed avoidance.

Moreover, we checked this possibility by analyzing the records of those 54 patients who were excluded from the study because of the longer time elapsed between the onset of panic disorder and our first observation. Although they were not administered the entire protocol, the descriptive reports of their first panic attacks were substantially the same as those of the study population: 70% of agoraphobic patients reported their first panic attack when in phobogenic situations, compared to 28% of patients without agoraphobia.

The association between public onset and agoraphobia merits special interest. An interpretation could suggest that a sort of subclinical agoraphobia might preexist clinical panic: phobogenic situations could then be regarded as potential risk factors for these people, thus enhancing the probability of having a panic attack. Lelliott et al. (1) suggested a role for an ethological factor (an evolutionary vulnerability to extraterritoriality), in addition to the biological and learning components of the disorder. While such a model is fascinating, it does not explain satisfactorily why such an onset is rare among patients with panic disorder without agoraphobia.

Another, simpler interpretation could be taken into account. The different psychological meaning of the context in which panic occurs might explain the evolution of the disorder. Experiencing the drama of an unexpected panic attack in settings in which, objectively, help is not available has a different psychological impact than experiencing the same symptoms in protected settings (e.g., at home). It is possible that undergoing such a stressful experience as having an attack in contexts in which one is helpless might affect the later course of the disorder. In this case the basic core of panic disorder would be the pathological evolution of panic, rather than panic itself.

However, in order to evaluate this possibility, as well as the model of Lelliott et al., it would be necessary to explore the settings in which panic occurs in those cases in which the attack fails to satisfy *DSM-III-R* criterion B for panic disorder because of its infrequent repetition or lack of the fear of having another attack (the so-called infrequent panic).

In conclusion, it seems that the results derived from these studies might be seriously biased by the sample selections and that community samples would be preferable.

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# Changes in *DSM-III-R* Axis II Diagnoses Following Treatment of Obsessive-Compulsive Disorder

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*Seventeen patients with obsessive-compulsive disorder and concomitant personality disorders were treated with pharmacologic and/or behavioral therapy and reassessed after 4 months. Nine of the 10 patients who responded to treatment for obsessive-compulsive disorder no longer met criteria for a personality disorder. Of the seven nonresponders, five continued to meet criteria for a personality disorder.*

(Am J Psychiatry 1992; 149:829–831)

Many patients with obsessive-compulsive disorder show comorbid personality disorders; rates of 49%–83% have been reported (1–4), although one group of investigators (5) found a prevalence of personality disorders no higher than that for a control population. A recent study (6) found that a group of patients with obsessive-compulsive disorder showed improved personality functioning, according to a self-rating scale, following brief treatment with clomipramine. This finding was related to treatment response, with responders showing the greatest improvement. The authors reached the conclusion that the severity of the axis I disorder may confound the assessment of a personality disorder.

The study we report was designed to examine the effects of improvement of obsessive-compulsive symptoms on comorbid personality disorders by using a standardized, structured interview, rather than self-report, to assess personality and diagnose personality disorders. Since we hypothesized that the diagnosis of personality disorders in many patients with obsessive-compulsive disorder is contaminated by features of the axis I disorder, we expected changes in personality disorders to follow symptomatic improvement of obsessive-compulsive disorder.

## METHOD

Twenty consecutive outpatients at an obsessive-compulsive disorders clinic and research unit who met the *DSM-III-R* criteria for obsessive-compulsive disorder according to the Structured Clinical Interview for DSM-III-R (SCID) (7) and who met criteria for at least one *DSM-III-R* personality disorder according to the Revised Structured Clinical Interview for DSM-III-R Personality Disorders (available from the first author on request) were contacted for inclusion in the study. The Revised Structured Clinical Interview for DSM-III-R Personality Disorders is the latest version of an extensively studied and reliable instrument for determining axis II diagnoses (8). The raters for this interview were instructed to challenge subjects who endorsed items, asking that they be certain that such traits were unrelated to their obsessive-compulsive disorder. The Yale-Brown Obsessive Compulsive Scale (9) was administered by each patient's attending psychiatrist on initial evaluation and again after 4 months of behavioral and/or pharmacologic treatment as a measure of clinical response. At follow-up the Revised Structured Clinical Interview for DSM-III-R Personality Disorders was conducted by the same research associate who administered it the first time; this person was blind to the patient's treatment response. The raters for both the Yale-Brown scale and the Revised Structured Clinical Interview for DSM-III-R Personality Disorders were trained at seminars conducted by the authors of these instruments and/or with video instruction, and at rating meetings held by the clinic in conjunction with other studies.

Seventeen patients (10 women and seven men) agreed to participate. They ranged in age from 19 to 61 years (mean=38.4 years, SD=12.2). All patients had suffered from obsessive-compulsive disorder for at least 2 years,

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**TABLE 1.** ***DSM-III-R*** **Axis II Diagnoses and Obsessive-Compulsive Scores of 17 Patients With Obsessive-Compulsive Disorder Before and After 4 Months of Pharmacologic and/or Behavior Therapy**

| | | | Personality Disorder Diagnosis[a] | | Obsessive-Compulsive Score[b] | | |
|---|---|---|---|---|---|---|---|
| Patient | Sex | Age (years) | Before Treatment | After Treatment | Before Treatment | After Treatment | Percent Change |
| 1 | F | 27 | Avoidant, dependent | No disorder | 26 | 1 | 96 |
| 2 | M | 32 | Obsessive-compulsive | No disorder | 21 | 16 | 24 |
| 3 | F | 19 | Mixed | Self-defeating | 13 | 13 | 0 |
| 4 | F | 32 | Mixed | No disorder | 15 | 7 | 53 |
| 5 | M | 27 | Avoidant | No disorder | 30 | 3 | 90 |
| 6 | F | 51 | Obsessive-compulsive | No disorder | 31 | 3 | 90 |
| 7 | M | 26 | Obsessive-compulsive | No disorder | 30 | 14 | 53 |
| 8 | F | 31 | Obsessive-compulsive | No disorder | 16 | 8 | 50 |
| 9 | M | 60 | Obsessive-compulsive | Obsessive-compulsive | 18 | 16 | 11 |
| 10 | M | 44 | Avoidant | No disorder | 16 | 5 | 69 |
| 11 | F | 61 | Obsessive-compulsive | Dependent | 33 | 15 | 55 |
| 12 | M | 50 | Obsessive-compulsive, avoidant, dependent | Obsessive-compulsive | 19 | 10 | 47 |
| 13 | F | 44 | Self-defeating | Self-defeating | 19 | 19 | 0 |
| 14 | F | 32 | Avoidant | No disorder | 18 | 10 | 44 |
| 15 | F | 46 | Mixed | Mixed | 21 | 20 | 5 |
| 16 | F | 41 | Mixed | No disorder | 31 | 10 | 68 |
| 17 | M | 31 | Avoidant, dependent | No disorder | 26 | 10 | 62 |

[a] Made with the Revised Structured Clinical Interview for DSM-III-R Personality Disorders.

[b] Yale-Brown Obsessive Compulsive Scale.

with a mean duration of 21.9 years (SD=16.2). The mean age at onset was 16.5 years (SD=8.4).

## RESULTS

Table 1 shows the complete results of the study. Pretreatment obsessive-compulsive symptoms were of moderate severity: the mean Yale-Brown Obsessive Compulsive Scale score was 22.5 (SD=6.6). Before treatment all subjects met the criteria for at least one personality disorder. Two subjects (patients 1 and 17) met the criteria for two personality disorders, and one subject (patient 12) met the criteria for three personality disorders. After treatment obsessive-compulsive symptoms were of subclinical severity: the mean Yale-Brown scale score was 10.6 (SD=5.7), a decrease of 11.9 points. After treatment the Revised Structured Clinical Interview for DSM-III-R Personality Disorders revealed that 11 patients no longer met the criteria for a personality disorder, while six continued to meet criteria (two for obsessive-compulsive, two for self-defeating, one for dependent, and one for mixed personality disorder).

Ten patients who showed a decrease of 50% or more in their scores on the Yale-Brown Obsessive Compulsive Scale after treatment were classified as "responders," and the remaining seven patients were classified as "nonresponders." Nine of the 10 responders to treatment for obsessive-compulsive disorder no longer met criteria for a personality disorder, while five of the seven nonresponders continued to meet such criteria (p=0.02, Fisher's exact test). Responders and nonresponders did not differ significantly in pretreatment Yale-Brown scale scores (t=1.78, df=16, p>0.10), age (t=0.36, df=16, p>0.72), or duration of obsessive-compulsive disorder (t=–1.03, df=16, p>0.32).

## DISCUSSION

The results of this study confirm previous findings (6) that *DSM-III-R* personality functioning may improve in some individuals with obsessive-compulsive disorder if there is improvement of the axis I disorder. Such results provoke serious questions about the nature of comorbid personality disorders in cases of obsessive-compulsive disorder. It is quite possible that the presence of such a debilitating disorder as obsessive-compulsive disorder, the symptoms of which extend into so many areas of everyday functioning, confounds the assessment of personality, as has been suggested in cases of panic disorder (10). If this hypothesis is true, then the concept of comorbid or concomitant personality disorders in some patients with obsessive-compulsive disorder is misleading.

Another interpretation of these results concerns the issue of diagnostic overlap. One consistent finding of clinical personality research in obsessive-compulsive disorder is the high prevalence of avoidant and dependent features (1, 4, 5). *DSM-III-R* classifies disorders with these features within cluster C of the personality disorders; patients are described as "anxious or fearful." Since anxiety and fearfulness tend to dominate the clinical picture of obsessive-compulsive disorder, it is not surprising to find such a preponderance of these patients with cluster C diagnoses. The personality diagnoses in our study group were, by chance, largely from cluster C. This is important to keep in mind when discussing the results, since cluster C may provide the most likely overlap with obsessive-compulsive disorder and thus might be expected to change more readily in response to significant decreases in the severity of the axis I disorder.

It is intriguing that despite having reminded subjects to describe themselves apart from their obsessive-compulsive disorder and despite actively challenging them when they endorsed items during the structured interview, we still found axis II diagnoses that depended on obsessive-compulsive disorder. Thus, it appears that discerning which symptoms are those of obsessive-compulsive disorder and which more accurately reflect personality is difficult, even for patients themselves. It is clear, though, that these symptoms—even those that are currently classified within the axis II personality disorders—can change with brief treatment.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

## PSYCHOTHERAPY

**Dynamic Psychotherapy: An Introductory Approach,** *by Marc H. Hollender, M.D., and Charles V. Ford, M.D. Washington, D.C., American Psychiatric Press, 1990, 215 pp., $31.00.*

In their preface to this book, Hollender and Ford state that they were "stirred by our memories" of Colby's *A Primer for Psychotherapists* (1). For many of us, Colby's book is a classic. Hollender and Ford's superb new book is a worthy successor; it is the distillate of their many years of intensive educational activities and clinical experiences. Hollender and Ford address the psychotherapy process directly and lucidly. Appropriately, they begin with a definition of psychotherapy and discuss its indications. They go on to provide guidelines for the beginnings of therapy and describe its fundamental principles and processes, technical interventions, and termination.

The incisive discussions of the many complexities of therapy are illustrated by excellent case histories and by the authors' attention to the pragmatic aspects of the day-to-day therapy process. For example, they diagram the desirable seating arrangements for the patient and the therapist, confront the issue of payment, and tackle complexities of insight-oriented psychotherapy such as interpretation and resistance.

Their emphasis on the therapist's summarizing his or her impressions of major points briefly at the end of each session is especially important; too often, therapy sessions end somewhat incompletely. There may be little consensus between the therapist and the patient about what has occurred during the session. In this respect, I wish that the authors had noted the outstanding 1964 article of Raymond W. Waggoner, Sr. (2), about one of his former patients who willed her diary to him. It contained her opinions of what had transpired during their therapy sessions 30 years previously. Dr. Waggoner compared them with his therapy notes and found that often there were vast discrepancies between what he and the patient thought had occurred.

Although several types of supportive therapy have been used by physicians since before the days of Hippocrates, the term *psychotherapeia* was introduced into the English language by a surgeon, Walter Cooper Dendy, in a paper that he read to the Medical Society of London in 1853. Hollender and Ford's description of dynamic psychotherapy would have pleased Dendy. They emphasize the central significance of the therapist-patient relationship and recommend ways for the therapist to structure it so that it can be of maximum therapeutic value.

Some of us differ a little from Hollender and Ford on just a few points. One is what I consider to be their lack of attention to the importance of the developmental history. Another is their lack of emphasis on the influence of the family of origin. I think that what happened in the patient's family of origin is often critical, especially during the recent decades when, for example, the problems of divorce, remarriage, and blended families causes concern about relationships and their stability. Notetaking is another point about which I differ with the authors. When the therapist is comfortable about taking notes, his or her doing so does not interfere with therapy, provided, of course, that the patient has been informed that the therapist's notetaking is routine. In fact, many patients regard extensive notetaking as an indication of the therapist's seriousness of purpose.

The authors are to be complimented for this important volume. The chapters on "Psychotherapy Combined With or Augmented by Pharmacotherapy," "Problem Situations and Difficult Patients," and "Termination of Psychotherapy" are particularly outstanding. Their book is more than just an introduction and guide to psychotherapy for students and residents. It will be of special value to the growing number of biological psychiatrists who have not had access to a short definitive volume of this type. The bibliography and both the name index and the subject index are accurate and comprehensive.

Drs. Hollender and Ford subtitle their book as "an introductory approach." They are modest. It will rank as one of the top three or four volumes on dynamic therapy in the English language. I think it should be required reading for residents during each of their years of training, and all of us will learn by rereading it every few years. Again, the authors deserve to be congratulated.

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**Interpersonal Process in Cognitive Therapy,** *by Jeremy D. Safran and Zindel V. Segal. New York, Basic Books, 1990, 270 pp., $27.95.*

This is a gem of a book that manages to accomplish a number of things as it pursues its stated intention "to initiate a process of conceptual and technical expansion in cognitive therapy that is informed by other therapy traditions" (p. 4). Along the way, the authors summarize many of the fruitful concepts developed in the areas of emotion, social motivation, and attribution therapy research. They integrate these concepts with an operational perspective on the patient-therapist alliance and give good clinical illustrations of how knowledge of cognitive concepts tied to interpersonal schemata can guide the therapist's appropriate interventions to effect patient change.

For the past decade there has been a growing call for expansion of cognitive-behavioral therapy and techniques beyond the limited view of the individual as a "working self." The authors have responded by partially encompassing notions of the self "as being" and better defining some of the constructs that go into self-organization. The text extends the cognitive-behavioral view into interpersonal experiencing and processing. In many places the dynamically oriented reader will find familiar concepts clarified and put into operational forms that complement the dynamic view as well.

In the introduction the authors lay out current conceptual problems viewed from the cognitive therapy perspective: how to view psychotherapy as a human encounter, how to clarify the process perspective, how to resolve whether supportive and insight-oriented therapies really differ, and how to integrate unconscious information processing into therapy.

The first third of the book then sets up the theses that 1) cognitive-behavioral constructs about the working self need to be complemented by an emphasis on the self as organized for continued attachment as much as it is organized for individual productivity, 2) it follows that change in these constructs is best brought about by correcting the attachment between patient and therapist, and 3) the cognitive-behavioral method shows how particular patient-therapist attachment interactions can lead to generalized changes in the patient's interpersonal schemata. The term "schema" is in some danger of becoming a buzz word these days to plug into one's language when discussing the multidetermined nature of experience, thought, and action. Here, however, the authors limit and define their use of the word to an interpersonal schema—the generic representation of self-other interactions that is elaborated from personal experience (p. 66). Its function is to reorganize the processing of events in the real world for the purpose of maintaining relatedness (p. 68). They postulate that maladaptive functioning perpetuated by faulty personal schemata produces corresponding maladaptive interpersonal exchanges. This leads to the kind of processing cycle in which, for example, an aloof, paranoid, suspicious person expects to be rejected or viewed in a guarded way by others and indeed induces such reactions by his or her behavior.

The rest of the book emphasizes how the therapist intervenes to correct such cycles of interpersonal exchange. The first task is to get the patient to identify those core elements which perpetuate specific cognitive-interpersonal cycles. The reader will find that much of this discussion resonates with dynamic theorists such as Luborsky and Strupp and is reminiscent of the triangles of people and conflict that Malan, Davanloo, and others (starting with Karl Menninger) have identified as a central focus of dynamic therapy. Clarification of the elements of a specific cycle starts an intervention process for the therapist. This intervention consists of participant observation, identifying interpersonal markers in the flow of patient discourse that indicate discontinuities in his self-organization, then clarifying these discontinuities and empathically "metacommunicating" about them.

The change process that is advanced here involves three mechanisms: 1) decentering—experiencing one's own role in constructing reality, 2) experiential disconfirmation—disconfirming dysfunctional beliefs about the self and others through new experiences, and 3) accessing action-disposition information—discerning aspects of one's own inner experience that have previously been out of awareness (p. 6).

Decentering involves teaching the patient how to step out of his or her experience to observe it and quickly step back in to participate. The functional emphasis of this collaborative operation is on making patients aware that they construct and can change the construction of their experience and that this perceptual skill can be brought to bear on distorted perceptions with practice. The authors provide a series of session excerpts that illustrate the need for a strong positive therapeutic alliance as a precondition to collaborative relating over such perceptual corrections. The therapist must also be able to monitor the patient's dialogue to identify and inquire after interpersonal markers that signal points for fruitful intervention.

Experiential disconfirmation requires, first, patients' awareness of the content of specific playful ideas from which they construe expectations. Second, self-observant disconfirming experiences of these ideas in an atmosphere that, third, promotes reconstruction of the maladaptive content in the specific interpersonal schema. The authors' discussion and the clinical examples they provide clarify and operationalize this process, which Alexander and French, of course, called "corrective emotional experiencing" many years ago.

Action-disposition information refers to the content carried in cognitive-affective-behavioral couplings that the self constructs. It is hypothesized that when some of these couplings are originally formed in reaction to a situation, their experiencing and implied consequences threatened patients' views of themselves or their attachment to others. Consequently, parts of these couplings were distorted, repressed, or assigned to memory as "not me" in the service of reducing stress. The point of accurately emphasizing and accepting such patient coupling in the therapy relationship is to allow the patient to reexperience and resolve such dysfunctional views or beliefs. Presumably, "as patients develop more feasible interpersonal schemata and begin to process affective information more fully, their verbal and nonverbal behaviors become more congruent and duplicitous communication ceases. They become more aware of, and are able to assume more responsibility for, their dysfunctional interpersonal patterns" (p. 195).

In summary, I came away from this book feeling that the authors had contributed much clarity to how one uses the therapeutic relationship to promote change in the "working self" aspects of one's internal schemata. They allude to and operationalize, sometimes without labeling or giving due credit, other constructs in the "self as being" that must be addressed during the change process—shifts of material from unconscious to conscious levels, working around and through defenses, balancing positive self-validating experiences against self-denigrating ones to change the self-reactive stance of one's dynamic self-concept, and so on. I am in great sympathy with this book and feel that it contributes to its stated aim to further "the integration of different psychotherapy systems [which] thus increases the possibility of understanding and working with important clinical phenomena by broadening the range of phenomena actually examined and by providing multiple perspectives on the same phenomenon" (p. 14).

This book is not for entry-level therapists because it presumes that the reader had received graduate training at the postdoctoral level and beyond. I could easily pair this book with Leston Havens' *Making Contact* (1) and say that, between the two, most of the current knowledge base for how one sets up the tactics of therapy dialogue is described.

## REFERENCE

1. Havens L: Making Contact: Uses of Language in Psychotherapy. Cambridge, Mass, Harvard University Press, 1986

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**Concise Guide to Psychodynamic Psychotherapy,** *by Robert J. Ursano, M.D., Stephen M. Sonnenberg, M.D., and Susan G. Lazar, M.D. Washington, D.C., American Psychiatric Press, 1991, 128 pp., $18.50.*

The attempt to reduce psychodynamic psychotherapy to a succinct 128 pages initially arouses a reviewer's skepticism. One can read industriously for years and find partially successful expositions but never achieve full satisfaction. There are a number of reasons for this, of course. Psychoanalytic therapy is a tremendously unwieldy, pluralistic, historical discipline that defies a concise and coherent rendering. Expositors of the field are limited by their individual origins, outlooks, loyalties, and, finally, limitations of vision.

This slim volume, designed to be carried in a pocket, is meant to convey the essence of psychodynamic psychotherapy. It comes nowhere near achieving it, but it manages to convey a lot of information that may be of value to the neophyte therapist. There are well-done sections on patient evaluation and countertransference as well as discussions of practical matters that all neophytes have questions about (phone calls, fees, and office decor). Chapters distinguish brief dynamic psychotherapy, supportive psychotherapy, and psychotherapy of the borderline patient. The book hews to a classical line with some nods toward object relations theory.

The flaws in the book are obvious to the more mature psychoanalytic clinician. The book attempts to teach psychodynamic psychotherapy while relegating psychoanalytic theory to the references. Nowhere are the reasons and goals of this treatment approach outlined or discussed. Neither is the book a manual of psychotherapy that teaches what one says to the patient. The authors say nothing about psychotherapy research and what the patient (or the therapist, for that matter) gains through a well-conducted, appropriately terminated psychotherapy. Although much is made of transference, the book could have benefited from a discussion of Luborsky's method, which helps the trainee to identify "relationship episodes" from which transference interpretations develop. Finally, one of the most difficult things that the novice therapist must do is not mentioned, namely, the lengthy and arduous process of learning to be a psychodynamic psychotherapist. What actual skills are precursors to psychodynamic technique? Where does one start? How long does it take? Why should one decide to do this in an era of resurgent biological psychiatry? What sort of person makes a good dynamic psychotherapist? These questions ultimately must be handled in actual training, supervision, and personal psychotherapy or psychoanalysis.

Sections of this book are cogently written and genuinely reflect the rich spirit and principles of classical psychodynamic psychotherapy. It is an easy read, and the clinical examples are well done. Perhaps the true measure of success is whether the trainee, using direction provided by the references, turns to meatier references (Freud, Greenson, Malan, Langs, Kernberg, J. Sandler, and others) and embarks on the lifelong quest of understanding what psychodynamic psychotherapy entails.

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**Hypnosis: A Jungian Perspective,** *by James A. Hall. New York, Guilford Press, 1989, 179 pp., $25.00.*

Dr. Hall, a well-known Jungian psychoanalyst, has written a remarkable book for the novice as well as the experienced practitioner. He provides fundamentals of Jungian analysis and shows the application of hypnosis. He establishes relationships among psychotherapy, hypnotherapy, the induction of trance as well as dream states, and analysis with active imagination. Successes and pitfalls are demonstrated with the use of personal anecdotes that can keep any reader amused and interested throughout the book.

In his introduction Dr. Hall points out that conceptualizing the essence of hypnosis is very difficult. It is not a commonly staged performance, nor is it a response to suggestion or repetitive stimuli. Hypnosis should be thought of as a movement beyond the conscious into the realm of the unconscious. Dr. Hall discusses the relationship of hypnosis to dream states and the use of hypnotherapy to express the content or "complexes" of the unconscious.

Although Jung subsequently abandoned the practice of hypnosis, Dr. Hall speculates that Jung would reconsider using hypnosis in today's context. In the summary of chapter two he begins to foreshadow the linkages of dream work and active imagination to hypnosis. He explains how these interactions can be applied to our understanding of the use of complexes by the psyche, stressing that the basic rule for employment of this technique should be as one therapeutic modality among others in a larger framework of clinical practice.

The subsequent chapters deal with basic concepts of the Jungian psychotherapy such as complex, self-image, transcendent function, and archetype. For a novice such as myself, this provides the enlightenment needed in preparation for the remainder of the book.

Throughout the mid-portion of this book Dr. Hall performs the difficult task of relating Jung's theory on the nature of the psyche to the function of hypnosis. In his discussion of transcendent function, Dr. Hall stresses that through the deep concentration of hypnosis and the development of an active imagination, a transcendent function is formed that allows us to explore the complexes of the subconscious.

The latter portion of the book deals with practical considerations in the use of hypnotherapy. These include the actual induction techniques and the issues of transference and countertransference that can arise during the development of a therapeutic alliance.

In chapter nine the author suggests that transference-countertransference interactions may be due to the "mythological overtones that are attached to hypnosis." Fears of being controlled or dominated by the will of the therapist lend themselves to strong transference. If these same myths are shared by the therapist, underlying fantasies of power may become manifest.

Dr. Hall concludes with "Clinical Integration: Applications of Hypnotherapy Within a Jungian Model." Here he describes how self-images are broken apart and reformed as a result of experiences. Through the use of hypnosis, an affect-bridge can be used to create or alter complexes in order to counterbalance pathologic complexes and thus alter the individual's concept of self.

This text offers a comprehensive yet concise discussion of the practical use of hypnosis in the context of Jungian psychotherapy. For the clinical psychiatrist involved with therapeutic hypnosis or the academic psychiatrist involved with the instruction of novices, this book is an excellent resource. For residents and medical students, it provides an excellent introduction to both hypnosis and Jungian psychotherapy.

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## SOMATIC THERAPY

**Handbook of Psychiatric Drug Therapy, 2nd ed.,** *by George W. Arana, M.D., and Steven E. Hyman, M.D. Boston, Little, Brown and Co., 1991, 185 pp., $22.50 (paper).*

This is the second edition of an extremely useful book that was first published in 1987. The authors have updated and expanded all chapters, but the total number of chapters remains at seven. The organization of the book consists of an introductory chapter reviewing the basic principles of prescribing psychotropic agents and a chapter on each of the major categories of psychotropic drugs. There is a separate chapter entitled "Other Agents," which discusses the use of drugs, such as verapamil and clonidine, that have been drawn into psychiatric use from different categories of drugs used for treating medical illnesses. The use of medications in different psychiatric disorders is comprehensively covered. This book has a problem-specific table of contents in the beginning that is extremely useful for quick reference. New compounds introduced into the United States, like clozapine, fluoxetine, and clomipramine, are included.

The authors have been successful in putting a lot of information succinctly into a small handbook. The chapter on antipsychotic drugs gives an overview of the historical aspects and chemical structures in addition to pharmacological aspects. Tables listing equivalent doses, comparative side effects, and available preparations of antipsychotic drugs are extremely useful in daily practice. The authors discuss the major side effects of antipsychotics and their treatment very elegantly.

The chapters on antidepressants and lithium similarly cover all aspects of their use in psychiatry and almost all clinical prescribing questions that arise, such as use in pregnancy or in patients with seizure disorders, and the usefulness of drug plasma levels. The tables and illustrations given in these chapters, again, are extremely useful. The use of fluoxetine and clomipramine as well as their mechanisms of action and side effects are well discussed. It might have been helpful to have information as well on fluvoxamine and sertraline, which are expected to be introduced for clinical use. The use of lithium, including special reference to the elderly, is well covered.

Chapter five, which deals with anticonvulsants, discusses all aspects of their use in psychiatry in a clinically useful fashion. Hematological and hepatotoxic side effects of carbamazepine and valproic acid, respectively, are extremely well discussed.

The chapter on benzodiazepines has all basic information and gives a nice description of the $\gamma$-aminobutyric acid$_A$ receptor as well as an exhaustive list of causes of insomnia. Sublingual use of benzodiazepines is a new feature I learned from this book.

The last chapter discusses the new drugs that psychiatry is acquiring from other areas of medicine, such as the use of clonidine in the treatment of akathisia and the use of verapamil in mania. I certainly welcome the inclusion of disulfiram, the most commonly used drug for alcoholism. The book includes a detailed account of its mechanism of action.

This book is of high technical quality. The editing is good, and typographical errors and misspellings are rare. I would like to point out especially that the comparative tables of different medications are excellent for quick reference. Precautions regarding the use of medications in the elderly are mentioned at appropriate places. Drug interactions are extensively covered. The bibliography is structured so that finding specific references is easy.

This book will prove useful to general psychiatrists as a quick and portable reference. It will also be extremely useful for internists and family physicians. Psychiatry residents should be using this book, as should medical students during their clerkship. I strongly recommend it.

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**Fundamentals of Monitoring Psychoactive Drug Therapy,** *by C. Lindsay DeVane. Baltimore, Williams & Wilkins Co., 1990, 267 pp., $25.95.*

Numerous guides to the use of psychotropic drugs are now available for the practicing clinician. Each has a particular focus and style, and each can be recommended for some uses or special interests. The present volume is another review of the pharmacology and use of psychotropic drugs. It is unusual, however, in that it is written by a pharmacist rather than a psychiatrist.

As one might expect, the strongest points of this book are in the pharmacological information provided on each psychotropic drug at the beginning of each chapter. For example, listed under the term "database" are the formulations for a drug, the basic pharmacology, and pharmacokinetics. There is also useful information on dosage regimen, therapeutic monitoring, and interactions. Although all of this information is readily available in any other standard psychotropic drug-treatment manual, it is nicely and usefully gathered in each section in this volume. Furthermore, the introductory sections on basic pharmacokinetics provide a useful review of the topic of pharmacokinetics for the practicing clinician.

The book is much less successful, however, in its clinical description of psychiatric patients and the practical guidelines for prescribing medications. Descriptions of clinical syndromes tend to be brief and relatively superficial, and the information regarding drug treatment of different syndromes is presented uncritically as reviews of other published literature. The reader often wonders whether the author has actually had personal experience in using drugs with patients and if he understands the many variations and ranges of response that patients will have that never appear in published research reports. Consequently, the clinical applicability of using psychotropic drugs has a rather mechanical and lifeless quality in this book.

The title of the book is quite misleading. A volume reviewing the topic of therapeutic drug monitoring and providing specific information to clinicians on this topic would be very helpful. However, the actual drug monitoring content forms only a small fraction of each section of this book. Consequently, the reader is impressed by the amount of information gathered together here but is unsure of how to use it. It is not a comprehensive or critical review of the psychopharmacological literature, nor is it as useful a clinical guide as many of the other psychotropic drug-treatment manuals. Perhaps its most useful niche is to provide basic pharmacological information about each psychotropic drug as well as the classes of psychotropic drugs in a readily accessible manner for quick office reference. It probably will be very useful for pharmacists and for nonpsychiatric physicians who need ready access to the pharmacological profile of psychotropic drugs. For the practicing psychiatric clinician, resident, or student of psychiatry, however, this volume will not be as useful as some of the other psychotropic manuals that are currently available.

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**Lithium and the Endocrine System,** *edited by F. Neil Johnson. Basel, Karger, 1988, 219 pp., $158.50.*

This book is the second of a series of volumes, Lithium Therapy Monographs, under the general editorship of Neil Johnson. This particular volume addresses itself to the effect of lithium on the endocrine system and adopts a hormone-by-hormone approach. Most of the chapters are devoted to the description of experimental findings in animals. As such, the book would not, I think, be of great value to clinicians seeking knowledge about the effects of lithium on a particular hormone or endocrine system. The one exception is the overview chapter on lithium-thyroid interactions (chapter 7). Information in the chapter should be well-known to most prescribers of this drug, but it does contain some useful practical information concerning the monitoring of thyroid function during lithium therapy. The remaining chapters do not contain much by way of practical information for the clinical psychiatrist. The volume would be of interest, however, to those engaged in research into the mechanism of action of lithium. This is primarily the stated aim of the volume set out in the editor's preface. The book succeeds in this aim, although it may have been improved by combining some chapters. For example, chapters 4 and 18, dealing with melatonin and pineal rhythms, are clearly related and complement one another.

This is most unlikely to be a volume of interest to clinicians, nor is it likely to be one that they would purchase for their personal libraries. The volume contains much of the current experimental data on lithium and the endocrine system and would be a worthwhile purchase for a university/hospital library. In summary, it is a highly specialized volume of interest primarily to researchers in the area.

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**Mechanisms of Drug Action on the Nervous System, 2nd ed.,** *by Ronald W. Ryall. New York, Cambridge University Press, 1989, 224 pp., $49.50.*

This monograph was first published in 1979. Because of a number of major advances in related fields since then, the author undertook the task of rewriting and reorganizing most of the book, the result being this second edition. The book has two general chapters ("Introduction" and "Techniques to Investigate the Actions of Drugs on the Nervous System"), two chapters on the peripheral nervous system ("Neuromuscular Junction" and "Autonomic Nervous System"), and eight on the CNS. The last category includes chapters on central neurotransmitters, the blood-brain barrier, general anesthetics, pain and analgesics, drugs acting on inhibitory amino acids, drugs for schizophrenia, mood disorders, and disorders associated with defined brain lesions such as Wilson's disease.

The author is a lecturer in pharmacology at the University of Cambridge. This book is intended primarily for undergraduate students in science and preclinical medical students. Based on his years of teaching experience, the author has sought to present a "story" about each class of drugs. On the whole, he has accomplished this task well. The entire book is quite readable, thanks to the use of simple but informative tables and figures and a deliberate avoidance of unnecessary technical jargon. Instead of citing numerous references throughout the text, the author has listed "selected reading" at the end of the book. In general, the author has done an excellent job of providing a concise but interesting summary of a vast and growing field.

In such a book, there is an unavoidable risk of oversimplification, sometimes leading to wrong generalizations. For example, while describing extrapyramidal side effects of antipsychotic drugs, the author states, "The dyskinesias are of several types. Least troublesome . . . [is] akathisia" (p. 187). In reality, akathisia is usually not included under dyskinesias; also, it is one of the most distressing side effects.

There are two important omissions in the book. One is deliberate and involves drugs of abuse for which "too little is known about their mechanisms to give a coherent picture" (p. xvi). I do not think that we necessarily know much more about the mechanisms of action of therapeutic drugs compared with the drugs of abuse. Another missing area is a discussion of altered pharmacokinetics and pharmacodynamics of the various drugs with aging. In view of the growing elderly population and the common use of psychotropic drugs in older persons, greater attention to this issue would be helpful. Perhaps such deficits could be corrected in the third edition of the book.

Overall, I believe that this is an excellent introductory monograph on the subject and is worth recommending to the intended readership, namely, preclinical medical students and undergraduates in other sciences.

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**Benzodiazepines in Clinical Practice: Risks and Benefits,** *edited by Peter P. Roy-Byrne, M.D., and Deborah S. Cowley, M.D. Washington, D.C., American Psychiatric Press, 1991, 227 pp., $25.00.*

This book is a multi-authored up-to-date review of the benzodiazepines, a widely used group of anxiolytic and sedative/hypnotic drugs. The first two chapters present an excellent review of the biological mechanisms and pharmacokinetics and pharmacodynamics of these drugs. Interested clinicians will discover that considerable gains have been made in understanding the binding of benzodiazepines to receptor sites in the CNS, mechanisms of tolerance and withdrawal, and the possibility that there are endogenous ligands in the CNS. Concepts of lipid solubility and differences between single-dose and multiple-dose pharmacokinetics and their clinical application are usefully described.

The second and largest section of this book deals with the clinical uses of benzodiazepines. Treatment of anxiety and depression, psychosis, acute stress reactions, and sleep are discussed. Clinical vignettes are provided at the end of each chapter to illustrate the drug's uses. Section three comprises three excellent chapters reviewing the cognitive and psychomotor toxic effects, dependence, withdrawal, and the abuse liability of benzodiazepines. Each is a clearly presented review. Although relevant research literature is cited for illustrative purposes, these chapters are also not comprehensive or critical literature reviews.

The fourth section of the book discusses special issues and the uses of benzodiazepines in special populations: treatment of the medically ill, the use of benzodiazepines combined with behavioral treatment and psychological treatment, and the use of benzodiazepines in the elderly. All are well presented and useful for the clinician. The chapters are practical rather than comprehensive or critical literature reviews.

Overall, this volume provides an excellent clinical companion to the American Psychiatric Association Task Force report *Benzodiazepine Dependence, Toxicity, and Abuse* (1). If there is any complaint, it is the lack of an index. Since there is so much clinically useful information, the absence of an index is both surprising and somewhat annoying. Apart from this reservation, this well-edited review is recommended for clinicians.

## REFERENCE

1. Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990

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*Boston, Mass.*

## STRESS AND ANXIETY

**Posttraumatic Stress Disorder: Etiology, Phenomenology, and Treatment,** *edited by Marion E. Wolf, M.D., and Aron D. Mosnaim, Ph.D. Washington, D.C., American Psychiatric Press, 1990, 264 pp., $39.50.*

Using as core material data presented at the May 1989 meeting of the American Psychiatric Association as well as the results of studies undertaken by other research scientists, the authors gathered in this book present a comprehensive volume on the state of the art regarding posttraumatic stress disorder (PTSD). Major topics include nosologic issues, vulnerability to the disorder, dissociative mechanisms, the applicability of the resilience hypothesis for predicting prognosis and future outcome, reliability and validity issues, potential biological and psychoneuroendocrinological markers, comorbid disorders (e.g., borderline personality disorder, major depression, anxiety disorder, panic disorder, alcoholism or other substance abuse disorder, and factitious PTSD), premorbid predictors (e.g., psychopathology, antisocial behavior, socioeconomic status, and insecurities about masculinity and independence), psychosomatic symptoms, the effect of repeated exposure to combat activities, stress-induced analgesia, PTSD in response to major disaster, treatment modalities (e.g., antidepressant medications and individual and group psychotherapy), and forensic issues.

In large part, because of the still relatively early stage of development of knowledge in the field, many issues require extensive further investigation. One problem is the lack of reliability and validity estimates of a number of PTSD scales. It is interesting that no reliability estimates of any of the PTSD scales are reported in this volume. However, the chapter by Julia Frank et al. reports having "data showing excellent interrater reliability for diagnosing PTSD, using the SCID and *DSM-III-R* criteria." Relating this to specific guidelines for interpreting clinically and statistically acceptable levels of reliability estimates, Sparrow and I (1) and Fleiss (2) would define kappas or intraclass correlation coefficients of 0.75 and beyond as "excellent." A second problem is the manner in which the diagnosis of PTSD is made—structured or semistructured interview formats are usually regarded as providing more reliable and valid diagnostic information than self-report instruments. A third problem involves the challenging issue of comorbidity. Matthew Friedman reports some very valuable work in this area; he applied biological criteria for differentiating PTSD from both major depressive and panic disorders. Although using a different model, this work parallels that of Steinberg (3), who, in a related field, provided very specific criteria for differentiating one of the dissociative disorders (depersonalization) from a number of other disorders with which it is sometimes confused (e.g., depression, schizophrenia, substance abuse, seizure disorders, and organic illnesses). Finally, more well-controlled, double-blind clinical trials with appropriately large samples need to be conducted to assess properly the efficacy of various proposed treatments of PTSD.

In conclusion, this book is as valuable for assessing the status of research in PTSD as for its pinpointing specific areas requiring further research. Because of its scope, it should be of interest not only to those with a specific focus on PTSD but also to the wider audience of mental health practitioners and research investigators. For example, readers interested in dissociative disorders would be interested in the chapter by David Spiegel and Etzel Cardeña, which conceptualizes multiple personality disorder as a chronic and severe form of PTSD. The book would also be of interest to those with interest in borderline personality, panic disorder, anxiety disorder, and alexithymia (4).

I hope that in the next decade a number of the challenging problems brought to light by this book can be resolved, so that sufferers of PTSD and related disorders will receive appropriate diagnosis and treatment for their afflictions. Jessica Wolfe and Terence Keane point out that one estimate of the prevalence of PTSD in the community is 1%, which is the same as the estimate for schizophrenia. In this regard, my colleagues and I have recently published a set of recommended guidelines for establishing the reliability and validity of neuropsychological disorders with low base rates (5).

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**Strangers at Home: Vietnam Veterans Since the War,** *edited by Charles R. Figley and Seymour Leventman. New York, Brunner/Mazel, 1990, 416 pp., $26.95.*

**Trauma and the Vietnam War Generation: Report of Findings From the National Vietnam Veterans Readjustment Study,** *by Richard A. Kulka, William E. Schlenger, John A. Fairbanks, Richard L. Hough, B. Kathleen Jordan, Charles R. Marmar, and Daniel S. Weiss. New York, Brunner/Mazel, 1990, 352 pp., $19.95.*

The climactic year of the Vietnam war was 1968, when more than one-half million U.S. combat troops were fighting in Vietnam. Oddly, that year *DSM-II* did not include a diagnosis encompassing combat stress. *DSM-I,* published during the Korean war, only a few years after the end of World War II, included the diagnosis of gross stress reactions, which subsumed combat-stress reactions. More recently, posttraumatic stress disorder (PTSD) was formalized as a psychiatric diagnosis with the publication of *DSM-III* in 1980, and PTSD will be even more keenly redefined in *DSM-IV*.

The attitudes of U.S. servicemen and women and their compatriots have changed remarkably from the years of our nation's military entanglement in Southeast Asia to our more recent victory in Southwest Asia. What remains is that the United States has fought wars and that warfare, by definition, is traumatic, leaving a group of citizens emotionally and physically wounded by the experience. *Strangers at Home* and *Trauma and the Vietnam War Generation* are books in the Brunner/Mazel Psychosocial Stress Series. Fundamentally, each is about the Vietnam war and its emotional aftereffects on the individual soldier and our society collectively. Even though both books focus on the Vietnam experience, the audiences of each do not necessarily overlap.

*Strangers at Home* was originally published in 1980, the same year the diagnosis of PTSD was introduced, and has now been updated. It is an edited collection of well-written chapters spanning the war's psychological, sociological, political, and legal effects on the men and women who fought it. Most of the authors are Ph.D.s, and several have served as combatants in Vietnam.

The book is efficiently organized for ready reference and divided into three major subsections: War and the Warrior, The Returning Veteran, and Government Policies and the Veteran. Within each section are individual chapters with easily identified subsections. The first section emphasizes oral histories and the combat environment, and the second examines the transition and alienation faced by returning veterans. The last section underscores the struggles and successes of veterans, emphasizing legal problems, activism, and substance abuse and mental health programs. Conveniently, readers seeking specific information can page through the table of contents and quickly identify areas of interest. Each chapter is self-contained with cohesive transitions and a homogeneous tone not often found in multi-authored texts.

*Strangers at Home,* unlike *Trauma and the Vietnam War Generation,* is not heavily weighted in graphs, charts, and abbreviations. Both books, however, like many focusing on PTSD, are embellished with numerous firsthand reports of battle, loss, betrayal, and abandonment. Having fought in Vietnam as a Marine officer and later serving with the Marine Corps as a Navy psychiatrist in the Gulf War, my experience has lead me to become suspect of the overly dramatized war stories that are occasionally encountered in PTSD therapy groups. A little like fairy tales, war stories are stories of exclusion that often begin with a "once upon a time" narrative style which invites exaggeration. For the most part, however, I feel the editor or authors were judicious in their choice of case reports and selected accurate accounts of war and alienation. These case studies emphasize ground warfare, specifically infantry combat, where the faces, sounds, and smells of battle are unnervingly palpable. (The stresses of air and naval warfare are equally intense but characteristically more abstract.)

With a different voice, *Trauma and the Vietnam War Generation* is a book shaped by the findings of the National Vietnam Veterans Readjustment Study. In 1983, the U.S. Congress directed a survey of Vietnam veterans to establish "the prevalence and incidence of post-traumatic stress disorder (PTSD) and other psychological problems in readjusting to civilian life." This text embodies the outcome of this study, which took more than 4 years and nine million dollars to complete. Among the important findings unearthed is the recognition that, during the years of the study, 15.2% percent of all male and 8.5% percent of all female Vietnam combat theater veterans suffered from PTSD. The National Vietnam Veterans Readjustment Study analyses of the lifetime prevalence of PTSD indicated that 30.6% of male and 26.9% of female theater veterans qualified for a PTSD diagnosis at some time during their lives. The text focuses on the study's findings and implications.

Governmental reports are typically laden with stilted language, making for wearisome reading, and the authors and editors of this book should be praised for transforming technical data into a text that is much more "reader friendly." Essentially, *Trauma and the Vietnam War Generation* is a book created from facts, statistics, and in-depth scientific research, making it ideal reading for only the serious student of the Vietnam era or professionals particularly interested in war-related PTSD diagnosis, treatment, and research. Each chapter begins with a concise commentary and a chapter overview; these are then amplified throughout the text by numerous clearly marked sections emphasizing didactic research.

For psychiatrists treating veterans, a close familiarity with PTSD and the character of the patient's military service is essential. These books are helpful and professionally oriented, discussing the impact of the Vietnam war on veterans. The diagnosis of PTSD or "Vietnam syndrome" is purposely viewed solely from the vantage point of that war, offering the double-edged sword of making these books excellent reading for the clinician with subspecialty interest in PTSD but an unprofitable choice for psychiatrists treating emotional traumas that are often equally personal and shattering but remain beyond the territory of war.

For a reader broadly interested in the Vietnam era, the war's veterans, and PTSD, I would first recommend *Strangers at Home.* The editor is a renowned PTSD scholar and has edited several books focusing on stress disorders among veterans. This book touches on the psychological aspects of ground combat and aptly addresses the returning soldier's alienation from a less than welcoming society. Of course, in a timeless way, estrangement shadows every warrior returning from war. In Homer's *Odyssey,* Ulysses was cursed: "God of the Sea, I beg you, punish Ulysses for this. Visit him with storm and shipwreck. Let him wander many years before he reaches home, and when he gets there let him find himself unwanted, a stranger." Tragically, in all wars, among the victors and vanquished, some warriors inevitably become strangers at home.

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**Anxiety and the Heart,** *edited by D.G. Byrne and Ray H. Rosenman. New York, Hemisphere Publishing Corp. (Taylor & Francis Group), 1990, 491 pp., $55.00.*

Probably almost as long as man has thought about the heart and heart disease he has also speculated as to the relationship between anxiety and heart disease. This important book draws experts from various parts of the field to present a synthesis of the findings in their area. The final conclusion, as summed up by Ray Rosenman, is, "In particular, the widely held belief that anxiety, cardiovascular reactivity, and stress responses play causal roles in the pathogenesis of hypertension and coronary heart disease increasingly lacks validity" (p. 478). For this summary alone the book is important. The writing style, with the exception of a few clinical chapters and the conclusions section, has the style and feel of a reference text. In fact, most readers will probably use it for this purpose. Each chapter is perfectly readable, however, and the book is well edited.

The book consists of five sections: Basic Concepts of Anxiety, Biological Approaches to Anxiety, Anxiety Disorders and the Cardiovascular System, Responses to Cardiovascular Illness and Patient Management, and Conclusions. The first section contains four chapters: "The Concept of Anxiety," "The Anxiety Disorders," "Generalized Anxiety Disorders and Panicogenic Syndromes," and "Assessment of State and Trait Anxiety in Cardiovascular Disorders." These chapters are straightforward, cover contents indicated by their titles, and appear to be written by authors with a deep understanding of each area.

The second section consists of three chapters—one on physiology, one on the neural regulation of the cardiovascular system, and one on the neurobiology of anxiety. These chapters are comprehensive and well-written. However, they are also highly technical. I imagine that they would be of most use to people actually doing research in these areas.

The third section has seven chapters. A group of chapters on anxiety and coronary heart disease, mitral valve prolapse, and cardiovascular reactivity seem to be a bit repetitious because each comes to the same conclusion—that there is no proven relationship between anxiety and heart disease. Each chapter, however, is carefully and thoroughly written and approaches the question from a slightly different angle. There are also chapters on silent myocardial ischemia, emotions and sudden cardiac death, and type A behavior. These are highly interesting chapters, although the relationship between anxiety and heart disease was again found to be small. The chapter on type A behavior concludes that a relationship between this behavior and heart disease is present, if at all, only in a subgroup (those type A individuals who are in stressful situations and who deny that they are under stress).

Part four consists of four chapters that relate to how psychological/psychiatric variables interact with the outcome of individuals who already have cardiac disease or hypertension. These chapters would probably be of value to clinicians working in these specific areas.

In the last section the two chapters agree on their main points. The overall conclusion appears to be that the closer and more rigorously the relationship between early anxiety and later heart disease is examined, the less evidence of a relationship is found.

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**Stress, Personal Control, and Health,** *edited by Andrew Steptoe and Ad Appels. New York, John Wiley & Sons, 1989, 323 pp., $67.50.*

Between 1900 and 1905, William of Occam put forth a maxim that assumptions introduced to explain a thing must not be multiplied beyond necessity. This attempt to trim off the unnecessary avoirdupois from human logic was later to be known as "Occam's razor."

With a price tag of $67.50 facing them, ordinary, run-of-the-mill clinicians unattached to the academic field, with the inexorable caseload that we normally carry, would find it hard not to be too zealous with Occam's blade in regard to this book. But that would be tragic because this is a great book with a wealth of data and insights embedded in a tundra of multilayered assumptions. This work is the result of the scholarship of 23 authors from the Netherlands, the United States, Great Britain, Sweden, France, and Germany representing public health and epidemiology, medical sociology, social psychiatry, experimental and clinical psychology, nursing, and animal physiology.

Started in 1983 as part of the Medical and Health Research Programme of the Commission of the European Communities concerned with research into the breakdown of adaptation, this book exhaustively covers topics in three broad areas. First is occupational aspects, focusing on the role of control in job settings and the influence of control on health. Second is the clinical perspective, focusing on the relationship of control to clinical problems such as pain, emotional disorders, heart disease, and coping with stressful medical procedures. The third is mechanisms relating stress to control, focusing on psychophysiological consequences of behavioral choice in aversive situations, the role of controllability in cardiovascular activation and cardiovascular disease, neuroendocrine correlates of control and coping, and social control in relation to neuroendocrine and immunological responses.

The postscript, by Andrew Steptoe, serves as the wrap-up. Despite his charming, proper British disclaimer ("The purpose of this chapter is not to provide a summary of material detailed elsewhere, nor to attempt an integration of data from the diverse scientific fields related to control"), Steptoe proceeds to do just that—with the flourish of a well-trained brandisher of Occam's razor. His diagram of the interactive model of stress (p. 311) helped me understand this book better. I read this book (after many months of tortured postponements) the second time around by starting first with Steptoe's chapter 15 and actually found the return to the previously boring pages enjoyable.

The psychological responses to stress are broken down into cognitive, affective, behavioral, autonomic, endocrine, and immunological. Behavioral control is explained as a result of a balance of forces called psychosocial demands and psychosocial resources. The intensity, chronicity, novelty/familiarity, predictability, and complexity of psychosocial demands are explored minutely. I thought the discussions of psychosocial resources and their impact on the need for control or belief in control and the subsequent mastery of stress were the most helpful to me as a clinician. These aspects include cognitive appraisal, psychological coping, social network support, previous experience, and personality and behavior patterns such as hardiness, neuroticism, locus of control, self-esteem, and type A behavior.

I enjoyed the discussions of learned helplessness and was particularly impressed by the observation that control over positive experiences is important. "The way you deal with small things affects the way you deal with big things" is a clinician's standard admonition. This aspect of self-determination suggests that "people may choose not to exercise control in certain situations, but nevertheless feel a sense of autonomy in their decision."

The understanding of fine nuances of levels of perceived and actual control and how they lead to ease or disease will certainly be helpful to employers and employees, dentists, nurses, and physicians alike at work and in their own personal lives. This book is "must" reading for all employee assistance program workers as well as those who are interested in primary and secondary preventive medicine.

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## BASIC BIOLOGICAL FUNCTIONS

**Sleep and Biological Rhythms: Basic Mechanisms and Applications to Psychiatry,** *edited by Jacques Montplaisir and Roger Godbout. New York, Oxford University Press, 1990, 236 pp., $49.95.*

The past 20 years have witnessed a large volume of research examining sleep and biological rhythms in psychiatric disorders, particularly depression. This interest has been spurred by the belief that understanding the mechanisms driving sleep and biological rhythms may lead to a better understanding of the pathophysiology of psychiatric disorders. Surprisingly, few books have comprehensively reviewed basic and clinical aspects of this research. It is in this context that *Sleep and Biological Rhythms* appears. The product is a slim but authoritative, well-written, and well-referenced volume.

This book apparently grew out of a symposium held at the University of Montreal. However, the chapters are not merely symposium proceedings, but scholarly articles discussing their respective topics. The book is divided into two major sections, the first dealing with biological rhythms and the second with sleep, with some understandable overlap between the two. In each section, basic science aspects are presented first, followed by human studies and applications to psychiatry. Although most of the chapters are reviews of previous research, several also present new data, research methods, and new hypotheses. Both sections of the book are well presented, but the first section is somewhat more successful at uniting basic and applied aspects.

The section on biological rhythms begins with a clear and concise description of the background of circadian rhythm mechanisms written by Robert Y. Moore. This is followed by Benjamin Rusak's chapter, which discusses different behavioral aspects of circadian rhythms and raises a number of important questions regarding animal studies of circadian rhythms and inferences drawn about these. The discussion focuses on entrainment mechanisms, pacemaker hierarchies, the complexity of "gating" mechanisms, and open- versus closed-loop homeostasis in biological rhythms. Roger Broughton's chapter discusses various rhythms in human sleep, including circadian, long ultradian, and short ultradian rhythms. Also presented are recent results using the extending sleep paradigm as a means of investigating these rhythms. The highlight of the first section of the book is Thomas Wehr's chapter on sleep and biological rhythms in mood disorders. This chapter not only provides a comprehensive review of past sleep research on mood disorders but also discusses hypotheses that have been advanced and offers a new hypothesis: that of sleep as a physiological analog of heat. The chapter also provides a thought-provoking discussion of methodological difficulties in this body of work.

The final three chapters in the first section (authored by Czeisler, Lewy et al., and Terman) discuss more specific methodological aspects of human circadian rhythms research. These chapters are likely to be of greater interest to investigators in the field, but they also provide a useful background for the more clinically oriented. Czeisler's chapter presents a more "classical" method of examining biological rhythms in humans, and Terman focuses on a recent experimental paradigm using simulated dawn and dusk regimens to treat patients with seasonal affective disorder. The chapter by Lewy et al. presents data supporting the use of melatonin as a circadian phase marker. Unfortunately, these authors tend to "personalize" their arguments by contrasting their findings with those of other research groups. This type of argument detracts from the information regarding their research findings, which is certainly interesting in its own right.

The second section of the book deals with sleep and its basic mechanisms. These chapters address REM sleep, including basic anatomy and physiology, and cholinergic mechanisms in particular. Gillin's chapter on the cholinergic REM induction test in psychiatry follows naturally from McCarley's basic discussion of brainstem mechanisms. Another one of the more "basic" chapters, by Krueger et al., gives a challenging model of how different sleep factors and sleep loci may interact, with a specific focus on immune mechanisms. The chapter itself is clearly presented and authoritative, but it would have been helpful to have followed it with a chapter on human clinical studies. For instance, recent research in psychoneuroimmunology and psychoneuroendocrinology are natural follow-ups to the discussion by Krueger et al., but they are not included in this volume.

The final two chapters of the book deal with insomnia and other sleep disorders. Mendelson presents an interesting hypothesis regarding the nature of insomnia in a concise and well-argued format. The chapter by Godbout et al. on narcolepsy and periodic limb movements during sleep is a helpful review, but its relevance to either basic sleep mechanisms or psychiatry is less evident than other chapters.

In general, this volume succeeds at its task of uniting basic and clinical aspects of biological rhythms and sleep research. However, it would benefit from a more precise definition of its audience and goals. As written, it would be most helpful to researchers in the area, although it is certainly very readable for interested clinicians. A second relative weakness is that the psychiatric aspects of the book deal exclusively with depression and mania and do not address other areas of psychiatric sleep and biological rhythms research, such as psychotic disorders, longitudinal studies, and studies of aging. Pharmacological research in human sleep and psychiatric sleep research are also restricted in coverage, dealing only with cholinergic, and more indirectly, $\gamma$-aminobutyric acid-ergic influences.

Despite these few relative weaknesses, *Sleep and Biological Rhythms* makes pleasurable and provocative reading for the psychiatric researcher and clinician with an interest in biological rhythms and sleep.

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**Anorexia and Bulimia: Anatomy of a Social Epidemic,** *by Richard A. Gordon. Cambridge, Mass., Basil Blackwell, 1990, 170 pp., $24.95.*

In this fascinating and well-documented book, Richard A. Gordon elucidates some of the major cultural factors contributing to the increase in prevalence of eating disorders in Western societies. The underlying philosophy of the book draws heavily on the work of anthropologist George Devereaux. The major characteristics of an ethnic disorder include an increased frequency of the disorder in the particular culture and core conflicts that are pervasive in the culture expressed in an acute form in the individual who develops anxiety and mobilizes psychological defenses. Devereaux views ethnic disorders as essentially highly patterned templates for deviance that elicit ambivalent responses from others.

Against this theoretical background, Gordon presents a persuasive argument for the idea that both anorexia nervosa and bulimia nervosa are ethnic disorders. The well-known demographic features of the eating disorders are listed: primarily women are affected, prevalence has increased since the 1960s, and it is more common in Western consumer-oriented societies and in the upper socioeconomic classes. The cultural changes that have occurred during the last 30 years are then described, including changes in the female role, a preoccupation with appearance and body image, and a cultural obsession with obesity and weight control. Each of these wide-ranging cultural changes is then examined in relationship to the development of eating disorders. The author suggests that the central psychological problem faced by patients with eating disorders is symbolic of a much wider cultural dilemma for women in general: women are still raised to please others and subordinate their own desires and strivings but are now also expected to be powerful and accomplished, tasks that require self-determination and assertiveness. The idea that femaleness has undergone a cultural devaluation is another dilemma for young women striving to compete in aggressive and competitive male-dominated educational environments and occupations. The author posits that obesity has come to symbolize not being in control of one's inner self.

In the last section of the book Gordon describes anorexia nervosa and bulimia as deviant behavior patterns that are immediately recognized by others in the culture. He cites Devereaux as stating that ethnic disorders follow the cultural dictum: "Don't go crazy, but if you do, you should behave as follows." The concept "wild weekend diet" of a popular weight-loss program is described as a template for bulimia. Anorexia nervosa and bulimia are viewed as an unstated rebellion against cultural expectations; this rebellion is paradoxically and secretly admired by other members of the culture who are also concerned with the societal dilemmas symbolically represented by the disorders. Gordon concludes that the eating disorders are essentially "antisocial social disorders" that are both an affirmation and a disavowal of society's esteemed values.

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*Reprints of Book Forum reviews are not available.*

# *Letters to the Editor*

## *Final Exit* as a Manual for Suicide in Depressed Patients

SIR: We have recently treated two patients who made serious suicide attempts utilizing suggestions contained in the book *Final Exit: The Practicalities of Self-Deliverance and Assisted Suicide for the Dying* by Derek Humphrey (1). This book, intended to be a guide to suicide for the terminally ill, has raised considerable controversy regarding its impact on those suffering from terminal physical illnesses. We wish to draw attention to its possible effect on suicidally depressed, physically healthy patients.

Mr. A was a 47-year-old man with two children and a long history of depression treated with antidepressant medication. A worsening financial situation led Mr. A to obtain a copy of *Final Exit* in order to learn the lethal dose of diazepam. He felt assured by the book that suicide was "his right" and comforted by the knowledge that his suicide attempt would succeed, since he took the book's recommended dose of diazepam and alcohol.

Ms. B, a 31-year-old woman, had a history of recurrent depression and two previous overdose attempts. She bought *Final Exit* "just in case" her depression should worsen. She found the book "comforting" because it provided "a certain way out if it became necessary." While experiencing increased marital discord her depressive feelings intensified. Feeling her depression was "terminal," with no hope of recovery, she made a suicide attempt using a plastic bag over her head and enough sleeping pills to ensure at least 2 hours of sleep, as outlined in the book. The patient stated that the book "took the emotions out of making a suicide attempt . . . it was like following a recipe."

Both of these patients, although unsuccessful in their attempts, had fully expected to die; and both were "comforted" in their decisions by the book, not only in regard to its guidance regarding a method but in its seeming to legitimize suicide. It is likely that these patients might have made these attempts without having read the book. However, it does seem to have been a facilitator and supporter in their considerations about suicide.

Although the book is intended for adults suffering from a terminal illness, our two patients with major depression mistakenly felt that the book was directed to them. This is partially understandable, since Humphrey does not devote much consideration to the impact of depression on the decision to commit suicide. He addresses the issue briefly when discussing the case of a depressed terminally ill patient who sought out a physician to aid him in his suicide attempt. He writes, "It would be judicious and fair for a physician to decline to help if the patient who is asking for assistance in suicide is clearly depressed and not so rational. That depression may be treatable" (pp. 129–130). Neither patient seemed aware of this. Within the entire book it might easily be missed.

Given our experience we recommend that psychiatrists consider the availability of this book and its possible purchase when determining the risk of suicide in their depressed patients.

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## Trichotillomania Treated With Clomipramine and a Topical Steroid

SIR: We recently observed a patient with trichotillomania respond to the combination of clomipramine and a topical steroid.

Ms. A, a 22-year-old woman, had a 7-year history of compulsive hair pulling which started after a "bad perm." The hair pulling frequency and intensity had fluctuated over the years. When first seen, Ms. A had several small bald patches behind the ears and at the crown, which were easily disguised. She had never had large bald patches. She reported having an irresistible impulse to pull her hair and felt unable to control herself. She reported an increasing sense of tension before pulling the hair, followed by gratification after pulling it. There was no other explanation for the disorder, since there was no apparent inflammation to the skin, nor were there other psychiatric disorders that could have explained the compulsion, such as schizophrenia. When first seen, Ms. A was taking 75 mg/day of clomipramine, prescribed by a local psychiatrist. She had been taking the medication for 4 months and reported that it had reduced the hair pulling by approximately 50%. Increasing her dose to 150 mg/day did not provide additional benefit. The dose was reduced to 100 mg/day.

Due to a complaint of pruritis, she was referred to our dermatologists. We asked whether they could prescribe something that might relieve this abnormal sensation. She reported that the itching would center on a single hair which she would then seek out and pull, providing relief. Fluocinolone solution (0.01%) was prescribed, and she was instructed to apply it to the affected areas twice daily. It was believed that this might reduce any inflammation and itching that might stimulate the hair pulling.

Ms. A reported that the tingling stopped within 24 hours after the first application. She continued to use the solution once or twice a day for several weeks and reported that the hair pulling virtually stopped. To test herself, she stopped the solution and experienced a return of the tingling. She returned to using the solution which again rid her of the sensation. She had been using the solution periodically (about once weekly) for more than 20 weeks and still felt that it was of great benefit.

Trichotillomania commonly starts in childhood and persists through adulthood; most hair pullers are women (1). Treatment of trichotillomania is generally disappointing (2) and has included psychodynamic psychotherapy, behavioral interventions, and psychotropic medication. In a double-blind study (3), clomipramine was superior to desipramine. In another (4), fluoxetine was not superior to placebo. There has been little discussion about dermatologic treatments, especially solutions applied directly to the areas of hair loss, particularly in those who report pruritis. Since a substantial minority of trichotillomania patients report these sensations (5), it may be that a multimodal treatment, including the use of topical agents, would be the most helpful.

We are interested in learning whether other clinicians have prescribed topical steroids for their patients, or have referred them to dermatologists who have prescribed them.

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## Clomipramine and a Case of Exhibitionism

Sir: We would like to report a development that we noted in a patient who had a rather severe, longstanding history of exhibitionism.

> Mr. A had been arrested and charged with indecent exposure on at least four separate occasions. Subsequent to his arrests he became depressed, expressed suicidal thoughts, and was hospitalized for relatively brief periods of time. He would then be followed with outpatient psychotherapy. Over the past 10 years he attempted to establish control over his behavior, only to have his exhibitionism recur and to return to the practices which brought him into conflict with the law.
>
> After his last arrest he was started on a regimen of clomipramine, 150 mg/day, and was followed in counseling for a period of several months. The patient reported a significant decrease in his desire to exhibit himself after he had been taking clomipramine for approximately 3–4 weeks at the prescribed dosage. In addition he reported that the clomipramine interfered with his ability to ejaculate while masturbating. He noted that he could fantasize about the forbidden activity but that he was unable or very infrequently able to be orgasmic. This resulted in a sense of frustration and prolonged masturbation fantasies without reward (masturbatory satiation). He also reported that when he did have an orgasm it was much less "explosive" than his normal experience.
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> During the course of treatment, the patient stopped taking his clomipramine for about 2–3 weeks. He noted the almost immediate return of strong wishes to exhibit himself. Upon restarting the medication these wishes again regressed.

While this is only a single anecdotal case observation, we thought it might be worthwhile reporting to readers of the *Journal* who may be interested in this problem.

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## Potential Interaction of LSD and Fluoxetine

Sir: We report a case of grand mal convulsions following ingestion of LSD in conjunction with a therapeutic regimen of fluoxetine.

> Mr. A, 16 years old, had an unremarkable medical history, notable for the absence of a seizure disorder, and had been maintained without incident on a regimen of fluoxetine, 20 mg/day, for approximately 1 year. About 1 hour after consuming the second of two doses of "blotter" LSD (and 3 hours after the initial dose), he developed marked stupor. Emergency services were summoned. In transport to the hospital, the patient was observed to develop an apparent focal seizure involving the left arm and face, which progressed to a grand mal convulsion and responded to 10 mg i.v. of diazepam.
>
> Physical findings upon hospital admission were unremarkable. A neurologic evaluation, including EEG and magnetic resonance imaging brain scan, performed 24 hours after admission was normal. Routine urine toxicology, including screens for phencyclidine, cocaine, and amphetamine, was negative. The patient reported having consumed approximately 30 doses of LSD during the preceding year, while compliant with his fluoxetine regimen, without adverse effect, but noted that this was his first experience with a double dose of LSD.

Our review of the literature uncovered a single claim in 1967 of convulsions associated with LSD use (1). Dista Pharmaceuticals reported seizures in 12 of approximately 6,000 patients participating in their preliminary trials, one case subsequent to a massive overdose of fluoxetine and several of the other patients having preexisting seizure disorders. We note with interest the long-established finding of enhanced serotonergic activity in brain preparations of rats exposed to LSD (2, 3), the serotonin-potentiating activity of fluoxetine, and the documented inhibition of epileptiform activity by serotonin (4, 5).

Several limitations in our data restrict the conclusion of the LSD/fluoxetine combination as being the cause of the convulsive episode. These include 1) absence of laboratory determination of the actual illicit substance involved (although the patient's recollections, prior to the interference of retrograde amnesia from the seizure, were of an altered state of consciousness and visual distortions similar to his previous experiences with LSD); 2) the patient's report that he had consumed the same combination (albeit with a considerably lesser quantity of the illicit substance) without incident; and 3) prior reports that fluoxetine alone may cause convulsions. In addition, the possibility of a factitious seizure cannot be excluded, although the absence of secondary gain eliminates a hypothesis of malingering.

Despite these qualifiers, the widening application of fluoxetine and the modest resurgence of LSD use in a subpopulation of adolescents raise the potential interaction as a matter of concern.

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## Neuroleptic Malignant Syndrome Induced by Low-Dose Haloperidol

Sir: Neuroleptic malignant syndrome is an uncommon and potentially fatal complication of the use of neuroleptic medications. It is characterized by fever, extrapyramidal symptoms, autonomic instability, altered consciousness, and elevated muscle enzymes (1). Haloperidol is the most common offending agent; as little as 2 mg/day of haloperidol has been reported to cause neuroleptic malignant syndrome (2). We report a case of neuroleptic malignant syndrome precipitated by an intramuscular injection of 0.5 mg of haloperidol.

> Ms. A, a 61-year-old woman with a 3-year history of dementia meeting NINCDS-ADRDA criteria for probable Alzheimer's disease (3), was admitted to a geropsychiatry unit for management of agitation, psychosis, and assaultive behavior. Attempts at behavioral control with haloperidol, at oral doses of up to 2 mg/day, and trazodone, up to 300 mg/day, were abandoned because of lack of efficacy.
>
> While taking no medications regularly (but receiving a maximum of 0.5 mg/day of haloperidol orally as needed for agitation), the patient was given a single intramuscular injection of haloperidol, 0.5 mg. She had never before been treated with a parenteral neuroleptic. Over the ensuing 48 hours, she developed fever (101.5 °F), tachycardia (maximum pulse 120 bpm), and progressive rigidity and lethargy, with her creatine phosphokinase level rising from normal to 1025 mg/dl. A medical evaluation including chest X-ray, urinalysis and culture, blood cultures, and lumbar puncture failed to indicate infection. Treatment with fluids, acetaminophen, and two oral doses of benztropine, 0.5 mg, resulted in full resolution within 72 hours.

This case indicates the potential of a single intramuscular dose of 0.5 mg of haloperidol to induce neuroleptic malignant syndrome. Contributing factors were age (4), moderately severe dementia (5), and agitation. Also notable was the response to anticholinergic medication plus supportive care. The use of anticholinergics to treat neuroleptic malignant syndrome remains controversial. We wish to emphasize the risk of even low-dose parenteral neuroleptics in susceptible patients.

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## Patients' Opinions Concerning Side Effects of Depot Neuroleptics

Sir: Patients who use neuroleptics often complain about side effects. These side effects are a major factor in patient noncompliance.

Lingjaerde et al. (1) described the UKU side effect rating scale. The authors noted that doctors and patients often had different opinions concerning the severity of side effects; they reported, moreover, that psychic side effects were at least as common as neurological (extrapyramidal) symptoms.

My colleagues and I have set up an outpatient service (2) for patients suffering from chronic or intermittent psychoses who use depot neuroleptics. Most of these patients have a diagnosis of schizophrenia. A weekly coffee group takes place which is designed to give counseling and supervise patients and their families. Medication and side effects are given broad attention here. Patients are considered competent persons and medication management is directed toward the gaining of information, insight, and acceptance and therapy-oriented discussion.

In family meetings psychoeducation is given to the patients and their families. These meetings include group discussion. In 1989, before a meeting concerning the subject of side effects took place, an inventory of the patient's individual side effects was made.

Items from the UKU scale were used when drawing up the inventory. Since *subjective* assessment is important for medication compliance, however (3), objective criteria were replaced by subjective statements concerning the degree of the experienced discomfort. This was classified on an increasing ordinal scale: 0=absent, 1=slight, 2=considerable, 3=extreme. Those patients who used various depot neuroleptics (but only a few anticholinergics) were highly motivated toward this investigation and 81% (44 patients) completed the inventory.

For each item, responders' scores were computed to determine which side effects gave the most subjective discomfort. This resulted in the following classification of side effects in descending order of inconvenience: 1) sleepiness/sedation, 2) asthenia/lassitude/increased fatiguability, 3) weight gain, 4) tension/inner unrest, 5) concentration difficulties, 6) akathisia, 7) depression, 8) diminished sexual desire, 9) failing memory, 10) tremor, 11) hypokinesia/akinesia, 12) orthostatic dizziness, 13) dystonia/hyperkinesia, 14) accommodation disturbances, 15) reduced salivation, and 16) rigidity. We concluded that side effects affecting psychic functioning were clearly a much more serious problem for these patients than side effects interfering with motor activity.

Since this could be the same in other patient groups, it seems desirable to pay more attention to the subjective burden of side effects. Moreover, patient participation is important when defining research priorities and models.

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## Distortion of Racial Identity and Psychosis

SIR: While interviewing patients on the "homeless" ward of a hospital, we noticed an interesting similarity among the delusions exhibited by five psychotic African-American patients: each patient's sense of racial identity was distorted within his or her delusional construct.

One man diagnosed with schizoaffective disorder claimed that he was actually "white" (i.e., Caucasian) and he knew this because "I have eyes; I can see." The other patients, all of whom were diagnosed as having schizophrenia, recognized that they were black, but each claimed to have been born white and then somehow transformed.

Paraphrased examples of their delusional ideas include the following: "My father colored me up and put castor oil in my hair to kink it up. I was originally blond." "I was born a white girl, but when I was five the dentist gave me a shot and then I went into our maid's stomach and came out a little black girl." "I'm actually Sicilian. My dark skin color is due to mixing olive oil with my food." "I was white when I came down on the spaceship, but before I left my color was changed by an injection."

The original purpose of these interviews was to introduce medical students to the psychiatric interview. Selection of patients was based on recommendations of attending psychiatrists who asked patients if they were willing to speak with students. The interviews took place during the summers of 1990 and 1991, and the patients were not in the hospital simultaneously for any significant amount of time; thus, communication among the patients as a factor contributing to the similarity of their delusions seems unlikely.

We performed a computer-based literature search on the MEDLINE database and the PsycLIT database looking for articles discussing a distortion of racial identity among psychotic patients. No such articles were found.

If psychotic patients with a distortion of racial identity are seen fairly often in the clinical setting, it is curious that such patients have not been discussed in the literature. Perhaps in this era of increased sensitivity toward cultural and ethnic concerns, there is reluctance to discuss such racially charged issues in the context of psychological conflict. However, understanding the foundation for this distortion of identity could be useful in treatment and helpful in appreciating the significant effect "minority status" may have on African-American patients.

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## Does the End Justify the Means?

SIR: Physicians in academic medicine are familiar with the term "publish or perish" which is a euphemism for survival in academia. Over the last decade funding resources for academic medicine have been decreasing at a steady rate; schools of medicine across the nation have to struggle to keep their various academic departments operating with adequate and experienced faculty. Now there is a new euphemism that is coming to the forefront: "get grants or else." The pendulum in academic medicine is swinging toward a vigorous push for faculty to devote their time to generating income through research grants. Physicians in academia get recognition and reward based on the number of publications and grants that have their names and university affiliations attached to them. Such a reward system is bound to convey to junior faculty the message that patient care and medical teaching are only for second-rate faculty (often labeled as "clinical faculty"), while a real faculty member is one who conducts research, is awarded grant money, and is building national recognition through prolific publications.

The oath of Hippocrates, traditionally sworn by every new graduating medical school class, specifically defines the duty of physicians as patient-centered professionals who devote their life to treating the ill and teaching the art and science of medicine. The current academic climate seems to have lost sight of the mission of a medical school, which is primarily to educate and train medical students to become physicians that are able to treat patients.

Junior faculty hoping for an academic career feel pressured to turn from patient care and student teaching to devote time primarily for research. Junior faculty are even instructed to make "protected time" (1) (i.e., time away from the demands of patients, students, and residents) their first priority. If this current trend in academic medicine continues, medical schools will no longer be able to meet the needs of patient care and academic teaching. Medical schools may be pressured to become research institutions where patients would be primarily evaluated as prospective research subjects, medical students would be instructed through self-study and computer-programmed courses, residents would be trained in acquiring skills for successful writing of grant proposals, faculty would survive only if their names were printed as authors in medical journals, and department chairmen would only be recruited on the basis of their national reputation.

Academic departments pressured by economic and political forces may be pushing faculty toward research to justify their dire needs for funding resources. The principle of "the end justifies the means" should not govern academic decisions. History has taught mankind that this principle has only brought short-lived successes and no long-lasting effect for those who practiced it. Academic medicine should be restored to its intended mission of teaching the art and science of medicine as a patient-care-centered profession that utilizes research to improve the quality of medical care rather than as a means to bring in more funding.

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## Diminishing Toxic Effects of Lithium Administration

SIR: Toxic effects of chronic lithium administration can be diminished by a simple change in diet, but until recently this effective treatment has only been available to rats. In 1975, Olesen and colleagues showed that polyuria, growth retardation, and mortality in rats with serum lithium concentrations of 0.6–1.2 meq/liter could be ameliorated by simply adding potassium to the standard rat diet, provided that adequate dietary sodium was available. Although the potential significance of this finding for prevention of lithium-induced polyuria and gastrointestinal disturbances in patients treated for bipolar disorder has been noted (1), the possibility that increasing potassium ingestion would also reduce the therapeutic actions of lithium engendered caution.

More recently, a colleague and I have reported that dietary potassium supplementation sufficient to prevent lithium toxicity in rats and hamsters did not alter serum lithium or potassium concentrations and did not interfere with a CNS action of lithium (delay of circadian rhythms) (2). Human patients may similarly benefit from potassium supplementation without loss of lithium's therapeutic effectiveness. In one case report (3), oral supplementation of 40 meq/day of potassium prevented cardiac repolarization delay associated with lithium treatment, without altering the serum concentration or therapeutic effectiveness of lithium. Several brief reports have shown that, in bipolar patients satisfactorily maintained on lithium, side effects such as tremor, edema, polyuria, and thirst could be reversed by addition of only 16–20 meq/day of potassium (4). This is a relatively small amount of potassium, and well within the range of normal dietary intake.

Most bipolar patients experience some adverse effects of lithium treatment. Treatment of side effects with diuretics or β blockers may alter serum lithium concentration or may lead to toxic interactions. A more conservative approach may be to encourage patients to increase intake of potassium-rich foods by 20 meq/day (e.g., two bananas, two large carrots, two cups of skim milk, or half of a honeydew melon or avocado) (5). Alternatively, 16–20 meq/day of a liquid or tablet potassium supplement may be prescribed, provided that the risks of hyperkalemia and potential irritation and ulceration of the gastrointestinal tract, particularly with potassium tablets, are considered.

Although some psychiatrists use potassium supplementation to improve lithium's low therapeutic index, this treatment approach has never been reviewed. I would appreciate any clinical observations on lithium and potassium interactions in psychiatric or nonpsychiatric applications.

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## Hysterectomy in Patients With Panic Disorder

SIR: The association between psychological distress and gynecological problems has long been recognized (1–4). We write to describe our finding that nine of 16 (56.3%) of our subjects with panic disorder as a primary psychiatric diagnosis reported having had a hysterectomy for various gynecological problems.

All our subjects, participating in a clinical trial for older adults, met the *DSM-III-R* criteria for panic disorder. The mean age of these Caucasian women, recruited by television and newspaper announcements, was 62.6 years, with a range of 56–76 years. All lived in the greater San Francisco Bay area and were of middle income socioeconomic status. Age at time of hysterectomy ranged from 22 years to 49 years, with the mean age being 37.7 years. All patients reported medical reasons other than cancer for the surgery.

The prevalence figures for hysterectomy show that until 1981, hysterectomy was the most commonly performed surgery in the United States, and by 1985, following that of caesarean section, it was the second most common (5). It also appears that by the time they are 60 years old, up to 37% of all women in the United States have had a hysterectomy (5). Our data, although from a limited sample, raise the possibility of a much greater prevalence of hysterectomy in patients with panic disorder. The literature suggests the possibility of such an association. For example, Gath et al. (3) reported that 150 patients with menorrhagia of benign origin who were referred for hysterectomy manifested significantly greater levels of anxiety than did women in the general population. Salter (4) also reported high anxiety in a sample of 102 patients referred for hysterectomy for problems other than malignancy. Our investigation is an attempt to further elucidate this association by studying it in relation to a specific diagnosis (panic disorder).

Despite our small sample size, our data seem to confirm earlier reports that there may be a greater than average prevalence of gynecological problems in anxious women. The question may be raised whether many of the hysterectomies performed in such cases can be prevented if these patients are assessed and treated appropriately for their panic symptoms. Our data, though preliminary, suggest the need for more detailed and systematic investigation in this area.

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## Freud and Homosexuality

Sɪʀ: In his review of *Three Essays on the Theory of Sexuality*, Alan A. Stone, M.D. (1) wrote of Freud's enlightened views about homosexuality. "It is unfortunate," he commented, "that gay psychiatrists have chosen to ignore this book and have made Freud a target of their criticism."

I, for one, did not ignore *Three Essays* (2, p. 139) or Freud's enlightened views, writing that "although Freud equivocated about whether or not homosexuality was in itself pathological, unlike contemporary psychoanalysts, he did not consider homosexuals 'sick' " (2, p. 3). I quoted an interview of Oct. 27, 1903, that was published in the newspaper *Die Zeit* in which Freud stated: "I am . . . of the firm conviction that homosexuals must not be treated as sick people . . . . Wouldn't that oblige us to characterize as sick many great thinkers and scholars . . . whom we admire precisely because of their mental health?" And I also noted his 1935 letter to an American mother: "Homosexuality is assuredly no advantage, but it is nothing to be ashamed of, no vice, no degradation, it cannot be classified as an illness" (2, p. 3). An emphasis on the constitutional basis of homosexuality recurs in Freud's writing (3, 4).

However, Freud also stressed environmental factors that analysis could investigate, since he was interested in promoting his new clinical technique. At one time or another he cited attachment to the mother, fear of castration, narcissism, a jealousy of younger and older brothers, and the absence of a strong father as "accidental" determinants of a homosexual object choice.

After his death, analysts appeared to be intent on removing any ambiguity in Freud's ideas about the nature and origin of homosexuality and decisively settled on a pathological model. One of the first to criticize Freud was Rado, who considered the idea of constitutional bisexuality to be biologically unsound and of little value in guiding future research. He believed that Freud's concept of an inborn potential for homosexuality led analysts to lower their therapeutic expectations in treating homosexual patients (5). Others soon followed with a clinical theory aimed at changing homosexuality to heterosexuality (2, pp. 15 and 109–127).

Institutes associated with the American Psychoanalytic Association have, in general, excluded openly gay men and lesbians from training, ignoring Freud and Rank's view that "a decision in such cases should be reserved for an examination of the individual's other qualities" (2, p. 6). This discriminatory admissions policy has until very recently deprived openly gay and lesbian psychiatrists of the opportunity to study Freud within psychoanalytic training institutes and has been the main reason that *Three Essays* has been "ignored" by gay psychiatrists.

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## Dr. Stone Replies

Sɪʀ: Dr. Isay may be correct in his belief that the "main reason that *Three Essays* has been ignored by gay psychiatrists" is because they were barred from admission to psychoanalytic institutes. However, Freud's works are read and studied by intellectuals around the world who have been excluded from psychoanalytic institutes. The organized psychoanalytic guild has no control over the legacy of Freud's ideas, and its members do not have a privileged reading of Freud's texts. Dr. Isay acknowledges that blanket condemnation of Freud and psychoanalysis by gay psychiatrists would be a mistake. I strongly agree. Most gay psychiatrists will not become "card-carrying" psychoanalysts in the future; hopefully, many will nonetheless read Freud's psychoanalytic interpretation of the human condition.

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## The Mind-Body Problem

Sɪʀ: I would like to comment on the article by Aviel Goodman, M.D. (1) on the mind-body problem. In the application of his theory to diagnosis, he suggests a double-track schema: one within the physical (objective) conceptual frame (which he says is what we have now with *DSM-III-R*) and another within the mental (subjective) frame. The objective type, he says, is useful for predicting responses to "physiological interventions" (p. 562), and the subjective diagnostic system may be of comparable value in predicting responses to psychological interventions.

This is unclear to me. Our current method of diagnosis is based partly on observations of behavior, including reports from observers, and the patient's report of his or her subjective state, such as mood and thoughts. When a man tells us that he believes the CIA has implanted a transmitter in his ear, in which of Dr. Goodman's frames does that belong? The fact that I and other observers listen to the patient's report of his thinking and can reach interrater reliability in completing a rating scale assessing delusions, would place it in the realm of indirect, objective knowledge, using concepts of the physical world. However, listening to a description of a delusion is not the same as measuring the patient's blood pressure. It is deeply involved with the patient's subjective state. I find it impossible to distinguish realms in this illustration. Dr. Goodman says (p. 561), "In each system are some hypotheses and methods that are more valid and some that are less valid, *according to the criteria for validity defined within that system*" (emphasis added). This can become a slippery slope. Dr. Goodman states repeatedly that all these concepts, theories, and hypotheses must prove their pragmatic value, a position with which I wholeheartedly agree. When he speaks of separate criteria of validity, I wonder what he means. Does he mean that psychotherapy should be judged as useful or not according to criteria different from those for drug treatment? Why? If we wish to know if a treatment alleviated the symptoms of depression, and we assess symptoms before and after treatment, is that in the "objective" realm and appropriate for measuring the effect of drug treatment but not of psychotherapy? I see no basis for that. I see no basis for judging the efficacy of treatment differently according to whether it is physical or psychological treatment.

What differences in validity between his two realms does Dr. Goodman mean? I do recognize that we make decisions using different sorts of evidence. I will decide what is the melting point of lead differently than I decide who should be my friend.

The crux of the matter, I believe, is that we make intuitive and nonintuitive judgments, and we have to keep the distinction clear. Perhaps this is what Dr. Goodman means when he says that there are two types of validity. My point is that "objective science" can apply to questions about subjective states, e.g., do drugs change mood? Does psychotherapy do the same? We shouldn't give up attempting to validate treatments of subjective states with objective science.

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### Dr. Goodman Replies

SIR: Dr. Rifkin asks whether my formulation classifies patients' reports of their subjective states as subjective or objective. The report itself constitutes objective behavioral data that can be described in observational terms (e.g., "Patient reported feeling depressed"). I agree with Dr. Rifkin that "listening to a description of a delusion is not the same as measuring the patient's blood pressure." The significant difference here is between "listening" and "measuring." Listening involves much more than registering the statements that are being reported: it entails a whole range of thoughts and feelings that are experienced by the listener in the context of this interpersonal process. The experience of a delusion is subjective data for the person who is experiencing it, but the listener or observer has no direct access to these data. A verbal description of a delusion, when abstracted from the totality of the listening experience (or when read), is objective data. Other components of the listening experience, including the listener's sense of the speaker's relatedness, emotional tone, and intentions, are subjective data from the perspective of listener as subject. The distinction between subjective and objective is relative to a particular subject.

This brings us to the issue of validity. As Dr. Rifkin notes, "We make intuitive and nonintuitive judgments, and we have to keep the distinction clear." I postulate that intuitive judgments, which are based on subjective experience that can not itself be verified intersubjectively, are not all equally valid, and that there must exist criteria that can assist in distinguishing between more and less valid intuitive judgments. However such criteria can be formulated, I believe that they will be different from criteria for validity in the objective system, and that the difference will have much to do with different forms of evidence and/or processes of confirmation (as noted in my response to an earlier letter to the Editor [1]).

Issues concerning validity are related to the question of how the effectiveness of a psychiatric intervention is to be determined. While I agree that alleviation of symptoms must be considered in assessing the effectiveness of psychotherapy as well as pharmacotherapy, I do not believe that alleviation of symptoms is an exhaustive or even a sufficient measure of psychotherapeutic effectiveness. The benefits of effective psychotherapy extend considerably beyond relief of symptoms, and an adequate assessment of psychotherapy effectiveness will need also to address data in the subjective or intuitive realm. This need underscores the importance of criteria for validity of subjective or intuitive data.

In closing, I concur with Dr. Rifkin's final statement that "we shouldn't give up attempting to validate treatments of subjective states with objective science." Meanwhile, I would add that we also shouldn't give up attempting to formulate a subjective (or mental or hermeneutic) science that can directly address subjective states, intuitive judgments, mental processes, and meanings. And I do not view objective science and subjective science as mutually exclusive but, rather, as complementary perspectives, the relationship between which can most usefully be formulated as dialectical.

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### On Kleptomania

SIR: I read with great interest the letter by Michael Beldoch, Ph.D. (1) regarding my article on kleptomania. It was an excellent letter and I agree with Dr. Beldoch's finding that his patient derived her benefit in part from the perceived forbidden nature of the act and its relationship to early abuse and the notion of the transitional object. I have been encouraged by the positive response to ideas put forward in the review article regarding early traumatic experiences and thank Dr. Beldoch for his observations and contribution.

There is however, a statement in the letter, attributed to Simpson and Porter, that could possibly be misinterpreted and I would like to call it to readers' attention so it may be clarified. In my article, I quoted Simpson and Porter, who were discussing *self-mutilation* and not kleptomania, as Dr. Beldoch's letter could indicate. Thus, Dr. Beldoch's phrase "this behavior" in the first sentence refers not to kleptomania but to self-mutilation. This point, however, does not diminish the clinical relevance of Dr. Beldoch's thoughtful letter.

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### Phencyclidine and Schizophrenia

SIR: It was with great interest that I read the review article by Daniel C. Javitt, M.D., and Stephen R. Zukin, M.D. (1).

What the authors discuss and essentially depict, e.g., in figure 4 is basically the "glutamate hypothesis" of schizophrenia. It may have escaped the authors' notice that a group of scientists at the University of Ulm and later Würzburg, Germany, has developed this model of schizophrenia since 1980 and corroborated it in several neurochemical studies (2–6). This prior original work on the subject may be relevant to those who are interested in the glutamate hypothesis of schizophrenia.

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## Dr. Zukin and Dr. Javitt Reply

SIR: We thank Dr. Kornhuber for the opportunity to comment on the distinctions between the phencyclidine and glutamate models of schizophrenia. Our article was a review centered historically and logically on the phencyclidine model per se, which was first proposed more than 25 years ago, rather than upon excitatory amino acid neurotransmitters and receptors (the glutamate hypothesis). In an earlier paper (1) we reviewed the role of excitatory amino acids in neuropsychiatric illnesses including hepatic encephalopathy, neurolathyrism, and Huntington's disease, as well as schizophrenia, in which connection we cited Dr. Kornhuber's work. Glutamate is, of course, the major excitatory neurotransmitter of the cortex, used by over 80% of neurons (2). It is therefore difficult to envisage a generalized glutamatergic deficit without accompanying encephalopathic changes. Glutamate mediates its effects at at least five receptor types (3). Phencyclidine interacts with only one of these, the NMDA-type glutamate receptor. The thrust of the phencyclidine model is that dysfunction of neurotransmission at a specific receptor type can lead to clinical symptoms that closely resemble those of schizophrenia. It is possible that there are other specific abnormalities of glutamatergic neurotransmission associated with schizophrenia, and we await reports of Dr. Kornhuber's ongoing research with great interest.

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## Suicidality and the Young

SIR: The superb article by Herbert Hendin, M.D. (1) dissects suicidality across cultural, diagnostic, and symptom complex lines, explores the relationship between cognitive and affect based therapeutic approaches ("the affective state usually clarifies and structures the cognitive one"), and goes beyond labels to define therapeutic effectiveness.

Treatment implies a psychotherapeutic framework (however labeled or worked with by the therapist), and psychodynamics structure the meaning, the power, the direction, and ultimately, the therapeutic potential of the patient's connectedness to the therapist.

People commit suicide or attempt it when they are overwhelmed, have run out of other options, and exist in an emotional system that permits death as an option, that is attached to death or someone dead, or that keeps death alive as a presence in the family or cultural system.

In these systems, separation (meaning comfort, security, and survival in the separated state) is not achieved from family members alive and dead, especially the dead or sometimes martyr figures who represent them in the past, and individuation is against the family rules in the present. There is a secret unconscious affective symbiosis leading to developmental impasse in dealing with the existential condition of humankind ("To be or not to be"). Powerlessness in the face of loss is as intolerable as hopelessness and emptiness in the state of a felt incompleteness of the ego. Acceptance of mortality and individuality is a universal human developmental task, resolving cognitive awareness of nonbeing that conflicts with the unconscious for whom nonbeing or mortality is impossible. It is reworked during times of crisis, developmental milestones, and especially during adolescence. Some people who accomplish the acceptance of mortality/individuality seem immune to suicide, while others carry the potential like a latent virus.

Suicide is a crisis of attachment beginning in early experiences of symbiosis which preclude empathy, and ending in a transgenerational confusion of love and death (during adolescence, of love, sex, and death). One patient who committed suicide put it most succinctly when she wrote: "I am in love with death."

I believe, concurring with Richman (2) and others (3–5), that the treatment of choice for teen suicide crisis is family crisis intervention, brief family therapy with parameters described by Langsley (6). Family crisis intervention provides team-oriented sessions (two to six in number, 1–2 hours in length), immediate availability during the window of affective opportunity for the family, with a cognitive focus on differentiation, combined with, on the affective level, a kind of grief work (growth perceived affectively as grief) to deal with the affect whose suppression holds symbiosis and leads to developmental impasse. These sessions are usually highly and permanently effective. The only contraindication to this approach is cognitive unavailability, usually pharmacologically based, of the patient or other family members.

Statistics might improve with a wider range and a greater continuity of awareness and vigilance, a family-based first line of therapy breaking through individual and systems barriers, and a recognition that capacity for grief can be a way of achieving growth and that learning to mourn can be a defense against melancholia, all to the end of accomplishing a universal developmental task.

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### Dr. Hendin Replies

SIR: I appreciate Dr. White's kind remarks about my article on the psychodynamics of suicide, but he overstates the case for family therapy as the treatment of choice for suicidal youngsters. Certainly in some cases, particularly when suicide attempts represent frustrated efforts by young people to involve their families in their distress, family therapy can provide appropriate treatment. In cases where the relationship with the family is more impaired, and a young person may need to escape a destructive family structure, family therapy that includes the youngster being seen with his parents may be harmful and contraindicated. Therapeutic wisdom and clinical judgment are necessary in deciding how, when, and to what degree to include the family in treatment.

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### Nocturnal Temperature in LLPDD

SIR: The article by Sally K. Severino, M.D., and colleagues (1) on nocturnal temperature elevation in late luteal phase dysphoric disorder (LLPDD) clearly documented a significant difference between control subjects and patients in the hours just after sleep. Although none of the patients was actually febrile, the difference between the groups was striking. The authors gave a hormonal explanation for this phenomenon. In addition, they stated that this temperature difference was not noted if the patients were kept awake. However, they presented no data for the latter statement and it was referred to as "work in progress." Toth et al. (2) recently presented data that demonstrated a high incidence of endometrial infection in premenstrual syndrome (PMS) and further showed that treatment with an antibiotic led to significant improvement in symptoms. I believe it is possible that Dr. Severino and associates may have observed a temperature dysregulation which is secondary to endometrial infection. I am not sure what sleep deprivation does to the thermal dysregulation of infection, nor am I sure if the pattern observed matches the usual pattern of endometrial infection. At the low level of infection noted by Toth et al., there are probably few normative data for temperature dysregulation. However, I believe it behooves the authors to examine their patients for infection prior to hypothesizing merely an endocrine dysregulation as the source for the thermal differences between patients and control subjects.

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### Dr. Severino and Colleagues Reply

SIR: Dr. Lipman makes the interesting suggestion that the temperature elevation we observed in women with LLPDD may be "a temperature dysregulation which is secondary to endometrial infection." If the temperature elevation were an expression of fever, we would expect the temperature curves of patients and control subjects to diverge at a different time of day, as demonstrated by Hejl (1) who showed that the onset time of fever from bacterial infections occurs largely in the morning, beginning at 4:00 a.m. and peaking at 9:00 a.m. Hejl also showed that fevers due to bacterial infections were more common at ovulation than at other menstrual cycle phases. The highest absolute temperatures in our women occurred in the luteal phase and the lowest temperatures were in the preovulatory phase, in keeping with the known thermal effects of progesterone and estrogen, respectively.

The elevated temperatures we found occurred during the sleep period, not at a particular clock time. Furthermore, as we pointed out in our article, nocturnal temperature elevation has also been reported in studies of patients with depressive illness which included *men* as well as women (2).

We did not perform endometrial biopsies, but even if evidence of infections were found, the restriction of hyperthermic responses to the early sleep period would require explanation in terms of some physiological property of either the infectious agent or host.

Dr. Severino is currently collaborating with Dr. Toth in a double-blind, placebo-controlled study of women with LLPDD whose endometrial biopsies are positive for mycoplasma, chlamydia, and/or anaerobic bacteria who are treated with clindamycin and gentamycin. Should treatment lead to improvement of emotional symptoms, some additional hypothesis must then explain how a distant and localized infection causes the CNS symptoms of depression, anxiety, and anger. We suspect that this mechanism will involve brain gonadal hormone receptors that are common to both the hypothalamic thermoregulatory system and the limbic system. Although abnormal gonadal hormone levels have not been found in women with PMS/LLPDD, it may be that Dr. Toth's patients represent a subtype in which the mechanism of the CNS symptoms is some alteration of gonadal hormone levels due to local ovarian infection.

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## Fluoxetine and Serotonin in Autism

Sir: In his letter, Richard Todd, M.D. (1) speculated that therapeutic action of fluoxetine in autism may be related to effects on the serotonergic abnormalities in these individuals.

Whole blood serotonin is increased significantly in people with autism (2). Fluoxetine should theoretically increase serotonin further as it acts principally by inhibition of presynaptic serotonin reuptake. Therefore it is difficult to speculate that changes in serotonin levels were responsible for the clinical improvements seen in three of his four cases.

This is not the first time serotonergic compounds have been used in the treatment of autism. Stern et al. (3) found that *d*-fenfluramine (a compound subsequently shown to stimulate release and block reuptake of serotonin [4]) reduced blood serotonin levels in autistic children with variable clinical improvement, an equally confusing effect.

Interestingly, in the gastroenterological literature, both fluoxetine (5) and *d*-fenfluramine are prescribed to raise serotonin levels in the treatment of obesity.

It would be interesting to note if fluoxetine caused correction of hyperserotonemia in autistic patients. It may be that fluoxetine, like fenfluramine, has properties of increasing and decreasing serotonin in different circumstances or that both work by a different and nonserotonergic mechanism in autistic patients.

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## Elevated Cortisol Concentrations and the Diminished Prolactin Response to Fenfluramine

Sir: The recent report by Veronica O'Keane, M.B., and Timothy G. Dinan, M.D. (1) is an important contribution to the neuroendocrine literature, being the first investigation of hormonal responses to the *d*-isomer of fenfluramine in depressed subjects. Our group has also been concerned about the neurotransmitter specificity of the racemic (*d,l*) form of fenfluramine. We have recently found a significant correlation between increased levels of plasma homovanillic acid and both the prolactin and cortisol responses to that agent, suggesting that the endocrine responses to the racemate may be mediated, at least in part, by catecholaminergic systems (2).

In our study of hormonal responses to *d,l*-fenfluramine in depressed and normal subjects (3), we found that the blunting of the prolactin response in endogenous patients was dependent upon the elevated baseline cortisol levels in that group. Deakin (4) similarly found that basal cortisol concentrations were strongly and inversely predictive of the magnitude of prolactin responses to L-tryptophan. The findings of these two studies suggest that cortisol reduces prolactin responsivity to both L-tryptophan and fenfluramine. This hypothesis is consistent with a series of animal studies, including a recent report that cortisol rapidly reduces prolactin release in fish pituitary (5).

Such findings from clinical and animal studies indicate the importance of controlling for cortisol concentrations when investigating for prolactin responsiveness in depressed patients. We would be interested to know whether Dr. O'Keane and Dr. Dinan found any association between baseline cortisol concentrations and prolactin response to *d*-fenfluramine in their study.

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## Dr. Dinan and Dr. O'Keane Reply

Sir: Our results are consistent with those of Dr. Mitchell and Dr. Smythe in that we also found that the degree of prolactin blunting in depression in response to *d*-fenfluramine challenge is proportional to the elevation in basal cortisol levels, although this is not stated in the paper. With effective treatment the fenfluramine/prolactin responses tend to normalize in parallel with the drop in cortisol levels. In recent studies in our department we have found that artificial reduction in cortisol levels brought about by metyrapone (the 17B-hydroxylase inhibitor) enhances *d*-fenfluramine/prolactin responses in depressed subjects. In such studies we have pretreated depressed patients for 24 hours with metyrapone before conducting the *d*-fenfluramine/prolactin challenge test. These results provide evidence that cortisol does indeed inhibit the *d*-fenfluramine/prolactin response.

The major point of interest is the site or sites at which cortisol produces this inhibition. Dr. Mitchell and Dr. Smythe suggest that the inhibition may be at a pituitary level and this indeed could certainly be the case. However, it is possible that the elevation in glucocorticoids induces secondary changes in central serotonergic mechanisms. Work by De Kloet et al. (1) shows that altering glucocorticoid levels does induce significant alteration in central 5-HT receptor mechanisms. Further research is necessary to clarify the issue in depression.

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## Borderline Personality Disorder and Depressive Disorder

Sir: In their re-review of evidence relating to the relationship between borderline personality disorder and depressive disorder, John G. Gunderson, M.D., and Katharine A. Phillips, M.D., (1) presented four relevant hypotheses: I. depressive disorders are primary, II. borderline personality disorder is primary, III. they are unrelated, and IV. they are related in a nonspecific fashion. Their evidence adds further weight to the arguments against hypothesis I. They have also shifted their conclusions from favoring hypothesis IV, and secondarily hypothesis II, to favoring hypothesis III. However, their method of analysis is biased against hypothesis II and they overlook the possibility of a fifth hypothesis which essentially combines II and IV.

In order to demonstrate the bias in their analysis against hypothesis II, it is helpful to consider how personality disorders and biological disorders could be related. I have been working with a model of the brain as an information-processing system. As in a computer, there is physical hardware and informational software. When there are software errors in a computer, errors in information processing and instructions to itself and other hardware occur. An analogous situation occurs in the brain when distorted personality patterns result in emotional and behavioral dysfunction. This model provides a way of integrating biological, psychological, and social factors in the etiology of depressive disorders.

The authors argue that evidence from biological markers and family prevalence tends to refute hypothesis II. However, depression which has its origin primarily in personality patterns would not have the same biological markers and family prevalence as primarily biological depressions. If we accept the heterogeneity of depressions, the potential difference in these characteristics must also be accepted.

In their comorbidity argument, the authors pointed out that other personality disorders have an equal or greater likelihood of resulting in depressive disorders. While this does indeed indicate that a relationship between borderline personality disorder and depressive disorders is nonspecific, it does not negate the fact that there is a relationship. The authors also argued that some symptoms of borderline personality disorder and depressive disorders overlap, which may result in over diagnosis of depressive disorders in patients with borderline personality disorder. However, this is unlikely to account for all of the high lifetime incidence of major depression in borderline patients (80% lifetime history in one cited study [2]).

If patients with borderline personality disorder do have a greater incidence of depressive disorders as the evidence demonstrates, this must strongly refute hypothesis III. The nonspecificity of the relationship simply goes along with the view that any personality disorder will increase the incidence of depressive disorders because personality dysfunction is one factor in the heterogeneous, biopsychosocial nature of depression. What is supported in their studies then, appears to be a fifth hypothesis, i.e., that personality disorders, including borderline personality disorder, can be one nonspecific etiologic factor in depressive disorders.

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## Winter Seasonal Affective Disorder

Sir: Recently the *Journal* published a report of electrooculography (EOG) ratios in patients with winter seasonal affective disorder (1), in which the authors claimed that the EOG ratios of 19 patients were lower than those of 19 matched control subjects. If this result is confirmed in future studies, it may be a clue to the etiology of seasonal affective disorder.

However, in reading the article I noticed that the actual numbers used in the multivariate analysis of variance (MANOVA) were ratios of measurements rather than measurements themselves. The measurements themselves may have normal distributions, but one cannot assume that ratios computed from two distributions would necessarily have a normal distribution. If one inspects the distributions provided in figure 1 of the article, it is not clear that the distributions are bell-shaped and normal. Naturally, their conclusion would be less problematic if the N were sufficiently large, because of the central limit theorem, which states that as a sample becomes large, its mean becomes an unbiased estimate of the population mean regardless of what kind of distribution the data have. Unfortunately, an N of 19 is not sufficiently large (2), particularly if there are questions about the type of distributions in the samples. In addition, there may be correlations between the numerators and denominators in the ratios which might also compromise the validity of the statistical analysis.

Potential correlations between measurements also seemed to occur in the nonparametric test used by the authors. They performed a chi-square test on results from both eyes of all the subjects, assuming that each eye's EOG ratio should be considered uncorrelated with that of its paired eye. This assumption seems unlikely.

Discovery of a retinal abnormality in seasonal affective disorder would be important. However, the above considerations raise the possibility that the results rest on inappropriate statistical tests.

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## Dr. Lam Replies

SIR: The letter by Dr. Moul raises appropriate concerns about evaluation of statistical results. In fact, the distributions of the EOG ratios in our study did not violate assumptions of normality or equality of variance as measured by univariate homogeneity of variance tests (Bartlett-Box F=3.57, df=1, 3888, $p<0.10$, for right eye, Bartlett-Box F=2.78, df=1, 3888, $p<0.10$, for left eye). Similarly, the chi-square analyses remain significant even if each eye is considered independently ($\chi^2=3.89$, df=1, $p<0.05$, for right eye; $\chi^2=4.07$, df=1, $p<0.05$, for left eye). These data should address Dr. Moul's concerns about the statistical analysis for this study.

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## Part II of the ABPN Certification Examination

SIR: Recently, members of the American Board of Psychiatry and Neurology (ABPN) reported the results of their investigation of the interrater reliability of the "live" patient interview section of Part II examinations (1). I believe that the members of the ABPN Research and Development Committee should be commended for their foresight in undertaking this study, their industry in carrying it through, and their intellectual honesty in making their findings public. However, I would like to raise potentially serious concerns about the rating methods they chose and their interpretation of the data.

Examiners assigned candidates' performance to three categories: pass, fail, or condition. They calculated interrater agreement using a weighted kappa statistic and concluded that this establishes that the reliability of their assessment is in the "fair to good range," since kappa values are near 0.55. (By convention, kappa values less than 0.40 are interpreted to represent poor agreement beyond chance, values between 0.40 and 0.75 represent fair to good agreement beyond chance, and values greater than 0.75 represent excellent agreement beyond chance [2].) Unfortunately, the presence of a condition category needlessly introduces ambiguity into the analysis of the researchers' data. The circumstances of the examination are that candidates either pass or fail unconditionally. Applying the term "concordant" to the situation where both examiners assign the candidate's performance to the condition category is correct when calculating kappa but does not make sense when applied in a broader context. Consider three alternative ways of analyzing the data. Since candidates either fail or pass and there is no "conditional" grade given, some might argue that all forms of disagreement should be equally weighted. If one calculates the unweighted kappa of the total group in table 1, kappa falls to 0.41. One might assume that "conditional" means the examiner is thinking "pass, but I have some concerns about this candidate" or "fail, but I might be judging this candidate too harshly" and thereby collapse the conditional scores into either the pass or the fail groups. If everyone who receives a condition/pass or a pass/condition passes, kappa is 0.45. If everyone who receives a condition/pass or a pass/condition fails, kappa is 0.52. If data on the pass rate of the condition/pass, condition/condition, and pass/condition were known, it would be possible to calculate a kappa which is weighted by the pass rate, and it would probably fall between 0.45 and 0.52. These alternative ways of looking at the data support the hypothesis that interrater reliability of the patient examination is toward the poor side of the "fair to good range." Also, it would be interesting to know whether pairs of experienced examiners are more concordant than pairs of examiners "in which one is inexperienced."

Although the authors stated that a kappa of 0.55 is in the range of what might be expected for agreement in psychiatric research (3), it might be possible to obtain kappas considerably above 0.55 if, as the authors suggested, more explicit criteria are developed (4).

The board certification process is a serious matter which affects all American psychiatrists—economically, professionally, and emotionally. I believe that, in the best interests of both candidates and examiners, improvements in the examination process should be given the highest priority by the ABPN.

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SIR: The Research and Development Committee of the ABPN is to be commended for their diligence and commitment on assessing the reliability of the Part II (oral) examination in psychiatry. As an examiner for the ABPN over the past decade or so and as a participant in the study described, I am not in the least surprised at the Board's persistent efforts to examine themselves. At all times during the rigorous, and at times exhausting, 3-day examination period (yes, it is hard work and stressful for the examiners as well as the candidates), I have been constantly struck by the attempts at fairness; the thoughtfulness and dedication in the preparation and administration of the exams; the respect given to the candidates; the seriousness and dedication to the task at hand; and the willingness to sacrifice time, money, and sleep to assure the public that a Board-certified psychiatrist is, in fact, a qualified specialist. Given these tenuous, uncertain, and complicated times in American medicine's history, it is heartening to know that our Board is making exquisite efforts to document its testing procedures.

As the committee continues this effort I would raise the following question which might be factored into future research: does the selection process by which examiners are chosen skew the data in a falsely positive direction, i.e., might the interexaminer consistency appear greater than it is in reality?

Historically the examiners at the oral examination are divided into a number of teams. Quite frequently, the chief examiner of each team selects in advance those who will be on that team. And often those selected work, or were trained, at the same medical center as the chief examiner. This selection process creates a relatively homogeneous group team, the majority of whom are academic psychiatrists from the same institution who often view clinical psychiatry from a similar perspective.

Might there be some usefulness in reviewing the selection process of examiners? Would there be some value in "shuffling the deck" once examiners are selected, i.e., random assignment to teams? Is there any utility in attempting to select more private practitioners as examiners, since the majority of American psychiatrists are in private practice (1, 2)?

The ABPN's Research and Development Committee has suggested that more explicit grading criteria and more extensive rater training should improve test consistency. This makes good sense. In addition, by including diverse practitioners (e.g., private clinicians and public and administrative psychiatrists) as well as academics, greater team heterogeneity would be created. This addition, and randomizing the examiner teams, might well enhance the true reliability of the certification process.

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### Dr. McDermott and Associates Reply

SIR: We thank Dr. Barta and Dr. Granet for their comments on our study of the reliability of the Board certification examination. They each discuss different factors involved in reliability: the grading procedures and the examiners themselves. We will respond to these in turn.

It is reassuring that Dr. Barta's alternative ways of analyzing the data continue to produce results in the fair to good range of agreement beyond chance. While we appreciate his suggestion about eliminating the condition, or "ambiguous" grade, doing so for statistical purposes would distort the way in which the examination is actually conducted. As described in our article, the examination process consists of two pairs of examiners, each of whom independently assigns a grade of pass, condition, or fail to each candidate in two separate examination sections. This set of two consensus grades (pass, condition, or fail) from these two examination sections is later considered and compared in detail. For example, a candidate's performance may have been marginal in one of the two sections because of minor rather than major deficiencies; this condition grade is then resolved by comparing the detailed performance of the candidate in that section with the detailed performance in the other section. In the great majority of cases the condition in one section is raised to a pass when the candidate has passed the other section.

Dr. Barta correctly points out that the condition grade "needlessly introduces ambiguity into the analysis of the researcher's data." However, the condition grade provides an element of fairness to candidates who have not demonstrated clear evidence of passing performance in one section, even though it may confound the clarity of the data analysis. The final judgment about a candidate's performance is deferred until the performance in both sections can be evaluated in order to determine a final passing or failing grade for the examination as a whole. The way in which we have analyzed the data reflects that process. Unfortunately, we cannot answer Dr. Barta's question about whether pairs of experienced examiners are more concordant than pairs of examiners in which one is less experienced than the other.

Dr. Granet suggests another approach: randomized assignment to examiner teams to improve reliability. The development of national teams of examiners who conduct all examinations rather than teams assembled for each examination (the current procedure) might also improve reliability, but at the expense of diversity. Every effort is made to recruit qualified psychiatrists from different parts of the field into the examination process, and the Board gratefully acknowledges their sacrifice of time and income to help maintain standards for the field. Since there is no evidence that random assignment to teams would improve reliability, the Board has addressed Dr. Granet's question by setting common grading standards for *all* examiners through 1) required training for all first-time and senior examiners, and 2) a systematic study of *interteam* reliability. Should team differences emerge, additional examiner training will be introduced to maintain a standard examination in psychiatry.

We are reassured by both Dr. Barta's and Dr. Granet's concurrence that improvements in the examination process be given the highest priority. The ABPN is fully committed to ongoing evaluation and improvement of the examination process through the work of its Research and Development Committee.

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*Reprints of letters to the Editor are not available.*

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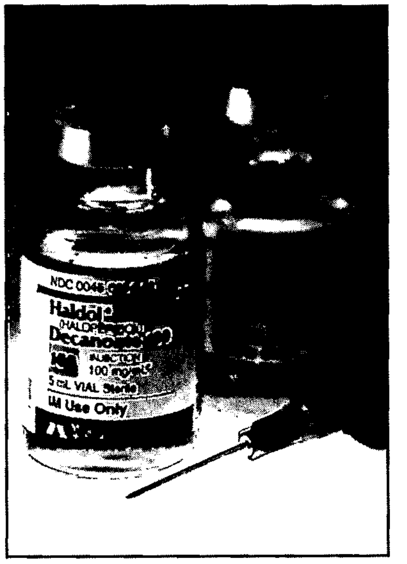
*Neuroleptic Malignant Syndrome (NMS):* A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.



*Usage in Pregnancy:* (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

*General:* Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, incuding haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used; (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

*Information for Patients:* Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

*Drug Interactions:* Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

*Usage in Pregnancy:* Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

*Nursing Mothers:* Infants should not be nursed during drug treatment.

*Pediatric Use:* Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

*CNS Effects: Extrapyramidal Reactions*—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

*Body as a Whole:* Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.**

**For information on symptoms and treatment of overdosage, see full prescribing information.**

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477 8/23/89

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Chronic schizophrenia: a 90s approach

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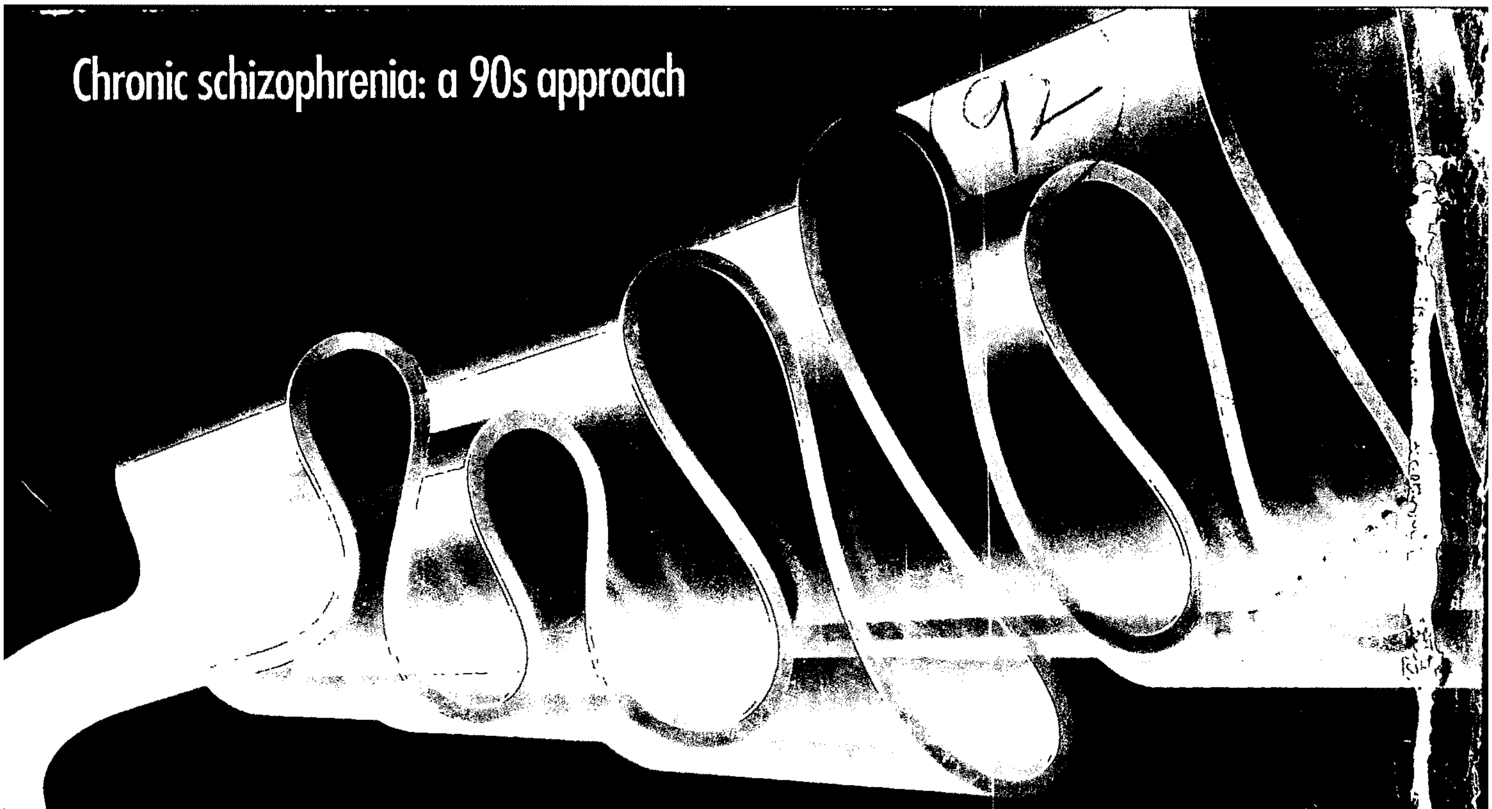

# A successful strategy for reducing relapse

## 74% reduction in relapse rates with haloperidol decanoate[1]

- ▲ Helps reduce the number of hospitalizations
- ▲ Convenient, once-a-month dosing

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL* (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

Please see brief summary of Prescribing Information on adjacent page.

Start depot therapy with **HALDOL® Decanoate 100**

(HALOPERIDOL) INJECTION 100mg/mL

Reference
1. Youssef HA. A five-year follow-up study of chronic schizophrenics and other psychotics treated in the community: depot haloperidol decanoate versus other neuroleptics. *Advances in Therapy.* 1989;6(4):186-195.

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